CORRECTED 21 MAY 2010; SEE LAST PAGE

Arsenic Trioxide Controls the Fate of the PML-RARα Oncoprotein by Directly Binding PML

Xiao-Wei Zhang,[1*] Xiao-Jing Yan,[1*] Zi-Ren Zhou,[2] Fei-Fei Yang,[3] Zi-Yu Wu,[3] Hong-Bin Sun,[4] Wen-Xue Liang,[1] Ai-Xin Song,[2] Valérie Lallemand-Breitenbach,[5] Marion Jeanne,[5] Qun-Ye Zhang,[1] Huai-Yu Yang,[6] Qiu-Hua Huang,[1] Guang-Biao Zhou,[7] Jian-Hua Tong,[1] Yan Zhang,[1] Ji-Hui Wu,[4] Hong-Yu Hu,[2] Hugues de Thé,[5,8] Sai-Juan Chen,[1,8]† Zhu Chen[1,8]†

Arsenic, an ancient drug used in traditional Chinese medicine, has attracted worldwide interest because it shows substantial anticancer activity in patients with acute promyelocytic leukemia (APL). Arsenic trioxide (As_2O_3) exerts its therapeutic effect by promoting degradation of an oncogenic protein that drives the growth of APL cells, PML-RARα (a fusion protein containing sequences from the PML zinc finger protein and retinoic acid receptor alpha). PML and PML-RARα degradation is triggered by their SUMOylation, but the mechanism by which As_2O_3 induces this posttranslational modification is unclear. Here we show that arsenic binds directly to cysteine residues in zinc fingers located within the RBCC domain of PML-RARα and PML. Arsenic binding induces PML oligomerization, which increases its interaction with the small ubiquitin-like protein modifier (SUMO)–conjugating enzyme UBC9, resulting in enhanced SUMOylation and degradation. The identification of PML as a direct target of As_2O_3 provides new insights into the drug's mechanism of action and its specificity for APL.

Oncogenic fusion proteins are a characteristic feature of many human leukemias and they often play a key role in driving the development and progression of the disease. These proteins arise when chromosomal rearrangements juxtapose two unrelated genes, and the resultant fusion gene produces an aberrant hybrid protein containing amino acid sequences corresponding to each gene. Because these oncogenic fusion proteins are selectively expressed in cancer cells, they have been extensively investigated as potential targets for anticancer therapies (*1*, *2*).

PML-RARα, a fusion protein found specifically in over 98% of human acute promyelocytic leukemia (APL), is produced as a result of a t(15;17) chromosomal translocation (*3*, *4*). It contains sequences from the promyelocytic leukemia protein (PML), a zinc finger protein whose function is not fully understood, and retinoic acid receptor alpha (RARα) (*4*). In vitro and in vivo studies have shown that PML-RARα is crucial for the pathogenesis of APL (*1*, *3*). Two drugs in clinical use for APL, arsenic trioxide (As_2O_3) and all-*trans* retinoic acid (ATRA), both act by promoting degradation of PML-RARα (*5*–*8*). When used as a combination therapy, these drugs lead to durable remission of APL (*9*). As_2O_3 induces degradation of PML-RARα and PML in NB4 cells, a human APL cell line (Fig. 1, A and B), by promoting a specific posttranslational modification (SUMOylation) of the PML moiety (*7*, *10*–*12*). The precise molecular mechanisms by which As_2O_3 regulates SUMOylation of these proteins remain obscure, however.

To investigate whether As_2O_3 directly alters the biochemical features of the PML proteins, we examined the effects of the drug on PML-RARα, PML, and RARα when these proteins were overexpressed in human embryonic kidney (HEK) 293T cells by DNA-mediated transfection (*13*). We found that as early as 10 min after exposure, As_2O_3 induced a shift of PML and PML-RARα, but not RARα, from the supernatant of cell lysates to the detergent-insoluble pellet (Fig. 1C) (*7*, *11*). After 30 min of As_2O_3 exposure, high-molecular-weight species corresponding to the modified forms of PML and PML-RARα were detected in the pellet fraction. Parallel experiments demonstrated the modifications to be the small ubiquitin-like protein modifiers SUMO-1, SUMO-2/3, and ubiquitin conjugations (fig. S1), consistent with previous studies (*11*). The rapid and specific effects of As_2O_3 on PML or PML-RARα pointed to a possible direct interaction of arsenic with these proteins. If arsenic binds directly to PML, it should be present together with PML in the detergent-insoluble pellet. We indeed observed that the arsenic content of the pellet from cells

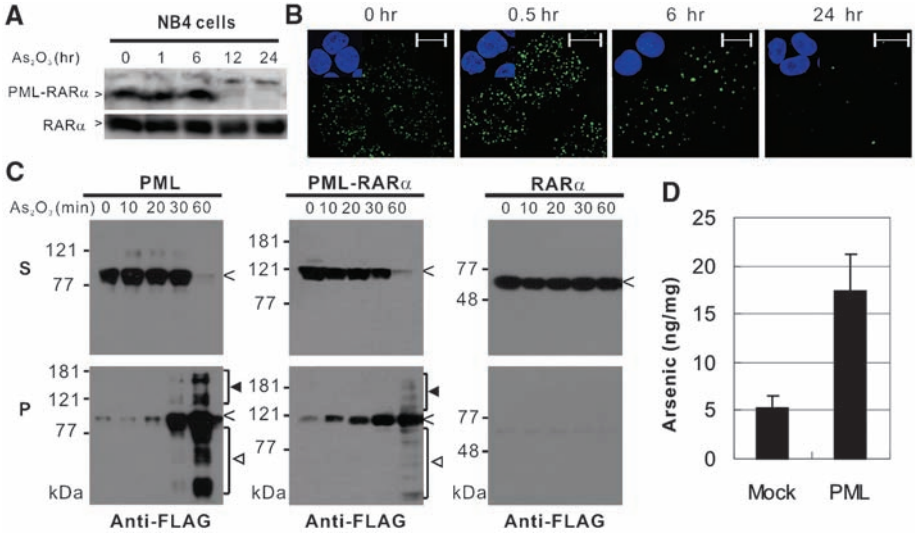

Fig. 1. The effect of As_2O_3 on the posttranslational modification and degradation of PML-RARα and PML is rapid and specific. (**A** and **B**) As_2O_3-induced degradation of PML-RARα in the APL cell line NB4 cells, as assessed by Western blotting with RARα antibody and immunofluorescence staining with PML antibody (green). The cells were treated with 1 μM As_2O_3. Scale bar, 10 μm. (**C**) A time-course study showing the effects of As_2O_3 on PML, PML-RARα, or RARα. (<) points to parental proteins, (▼) to modified proteins, and (▽) to degraded fragments. Transfected HEK 293T cells were treated with 2 μM As_2O_3 and then lysed in RIPA buffer and fractionated into supernatants (S) and pellets (P) by centrifugation. (**D**) The arsenic content of pellets from HEK 293T cells that had been mock-transfected or transfected with a vector encoding PML.

[1]State Key Laboratory of Medical Genomics, Shanghai Institute of Hematology, Rui Jin Hospital affiliated to Shanghai Jiao Tong University School of Medicine, 197 Rui Jin Road II, Shanghai 200025, China. [2]State Key Laboratory of Molecular Biology, Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences (CAS), Shanghai 200031, China. [3]National Synchrotron Radiation Laboratory, University of Science and Technology of China and Beijing Synchrotron Radiation Facility, Institute of High Energy Physics, CAS, Beijing 10004, China. [4]Hefei National Laboratory for Physical Sciences at Microscale and School of Life Sciences, University of Science and Technology of China, Hefei, Anhui 230026, China. [5]Université de Paris 7/INSERM/CNRS UMR 944/7151, Equipe Labellisée No. 11 Ligue Nationale Contre le Cancer, Hôpital St. Louis, Avenue C. Vellefaux, 75475 Paris CEDEX 10, France. [6]Shanghai Institute of Materia Medica, Shanghai Institutes for Biological Sciences, CAS, Shanghai 201203, China. [7]Laboratory of Molecular Carcinogenesis and Targeted Therapy for Cancer, State Key Laboratory of Biomembrane and Membrane Biotechnology, and Key Laboratory of Stem Cell Development, Institute of Zoology, CAS, Beijing, China. [8]The Pôle Sino-Français de génomique et de Sciences du vivant de l'Hôpital Rui-Jin, 197 Rui-Jin Road II, Shanghai, China.

*These authors contributed equally to this work.
†To whom correspondence should be addressed. E-mail: zchen@stn.sh.cn (Z.C.); sjchen@stn.sh.cn (S.-J.C.)

overexpressing PML was substantially greater than that of the pellet from control, mock-transfected cells (Fig. 1D).

Arsenic is a metalloid element known to exert some of its biological effects through direct interaction of the trivalent arsenite anion (AsO_3^{3-}) with the thiol groups of vicinal cysteines in target proteins (*14*, *15*). Notably, the N-terminal structure of PML that is retained in all PML-RARα isoforms harbors a cysteine-rich RBCC domain (*16*, *17*). This domain includes one RING domain (R), two B box motifs (B1 and B2), and a coiled-coil domain (CC). Contained within the PML-R and PML-B box are zinc fingers (ZFs), cysteine-rich structural regions that potentially could be involved in arsenic binding (fig. S2) (*17*–*19*).

To explore whether arsenic binds directly to PML and PML-RARα in cells, we used as probes two organic arsenicals with effects similar to those of As_2O_3, *p*-aminophenylarsine oxide (PAPAO) and ReAsH (fig. S3). PAPAO was conjugated to biotin (designated as Biotin-As) (*20*). Analysis by a streptavidin agarose affinity assay revealed that Biotin-As bound to PML and PML-RARα, but not to RARα, and that this binding could be attenuated by As_2O_3 or unlabeled PAPAO (Fig. 2A).

We next performed experiments with ReAsH, an organic arsenic derivative whose red fluorescence is quenched until its arsenic moieties bind to vicinal thiols in target proteins (*21*). PML localizes in a distinctive fashion to punctate PML nuclear bodies (NBs), whereas PML-RARα exhibits a microspeckled pattern (*7*, *22*). We found that ReAsH, like As_2O_3, induced the aggregation of PML NBs (Fig. 1B and 2B). Moreover, ReAsH colocalized with PML signals in NB4 cells (Fig. 2B), which suggested that ReAsH directly binds to PML-RARα and/or PML. This colocalization was attenuated by a pretreatment with As_2O_3 but not $ZnSO_4$ (Fig. 2B).

To further investigate arsenic binding, we transiently overexpressed proteins that were fused to EGFP (enhanced green fluorescent protein). ReAsH colocalized with EGFP-PML and EGFP-PML-RARα in a relatively specific manner (Fig. 2C and fig. S4). To clarify which region(s) of PML are involved in the interaction with ReAsH, we constructed various deletion mutants of the protein (fig. S2A). We observed that EGFP-PML 1–394 (containing the RBCC domain) was strongly labeled by ReAsH, whereas EGFP-PML ΔRBCC displayed no colocalization with ReAsH (Fig. 2C). There was almost no ReAsH colocalization signal detected in experiments with EGFP-PML ΔR, and the colocalization signal was significantly attenuated in experiments with EGFP-PML ΔB2. In contrast, EGFP-PML ΔB1 still showed significant colocalization with ReAsH. Collectively, these results suggest that arsenic directly binds PML through its RING domain, as well as its B2 motif (Fig. 2C).

The PML-R domain plays a central role in PML SUMOylation (*23*), and the structure of this domain has been determined by nuclear magnetic resonance (NMR) (*18*). We therefore used the isolated PML-R domain as a model to investigate the characteristics of arsenic interaction with the complete PML protein. We prepared recombinant apo-PML-R (PML-R without zinc) and determined arsenic binding activity by matrix-assisted laser desorption/ionization–time-of-flight (MALDI-TOF) mass spectrometry (MS) with the rationale that each molecule of arsenic bound to the protein should be identified by a mass increment of 75 (atomic mass of arsenic) as compared to the parental protein (*14*). In experiments involving a clinically relevant concentration of As_2O_3, we found that apo-PML-R bound to one or two arsenic (Fig. 3A). Optical absorbance of PML-R increased in the range of 250 to 340 nm with addition of As_2O_3 (Fig. 3B), which indicated that arsenic-sulfur bonds had formed (*24*). Extended x-ray absorption fine structure (EXAFS) and x-ray absorption near-edge structure (XANES) spectroscopy (*25*) indicated that arsenic tended to coordinate with three sulfur atoms from the three conserved cysteines in both PML-R-ZFs (C60, C77, C80 in ZF1 and C72, C88, C91 in ZF2), whereas zinc exhibited the typical tetrahedral coordination with conserved cysteine and histidine residues (Fig. 3, C and D, fig. S5, and tables S1 and S2). Consistent with this, the PML mutants with the double mutation C77/C80A (Cys^{77} Cys^{80} replaced by Ala) and C88/91A showed an attenuated affinity to arsenic and had no response to As_2O_3 modulation in terms of the pellet transfer and high-molecular-weight modification (fig. S6).

Proteins can adopt different conformations upon coordination with different metals, which affects both their function and stability (*26*). Circular dichroism (CD) showed that As-PML-R (apo-PML-R titrated with As_2O_3) adopted fewer secondary structures than Zn-PML-R (stabilized by zinc binding) (Fig. 3E), as previously shown with other proteins (*27*). NMR hetero-

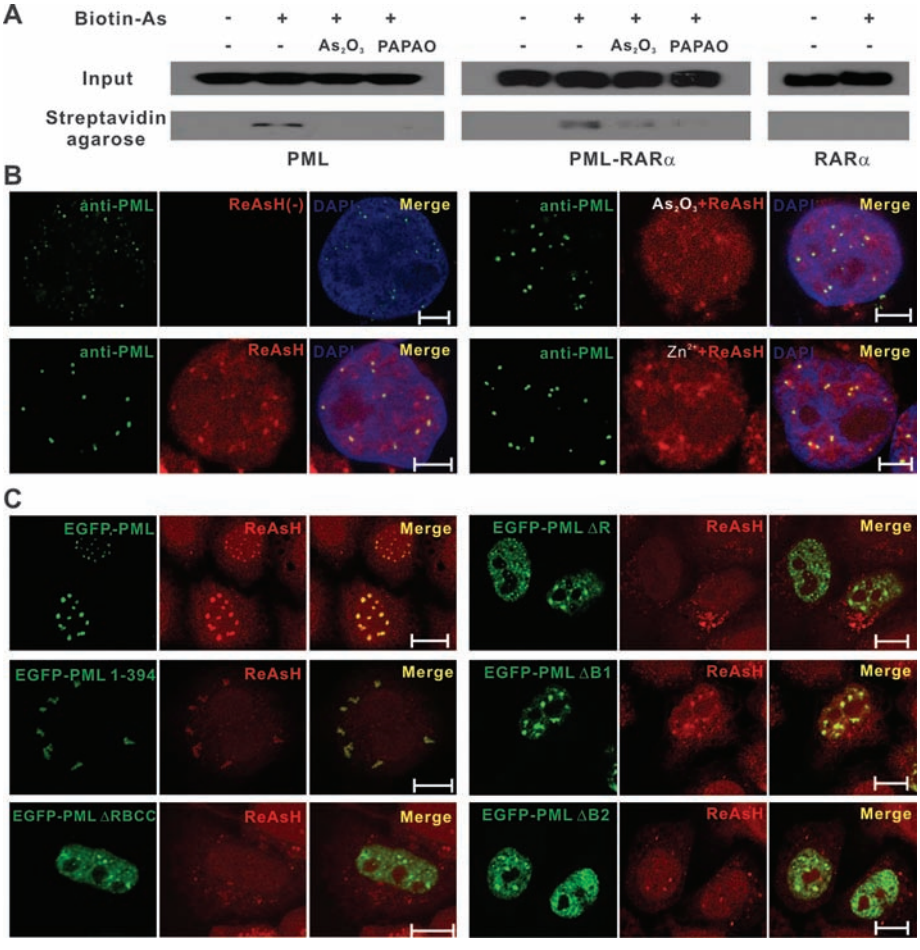

Fig. 2. Arsenic binds to PML-RARα and PML in cultured cells. (**A**) The arsenic binding proteins PML and PML-RARα, but not RARα, were identified in a streptavidin agarose affinity assay in which a biotinylated derivative of the organic arsenical PAPAO (Biotin-As) was used as a probe. (**B**) Colocalization of PML and PML-RARα with the fluorescent organic arsenical ReAsH in NB4 cells. As_2O_3+ReAsH, pretreatment with As_2O_3; Zn^{2+}+ReAsH, pretreatment with $ZnSO_4$. Scale bar, 5 μm. (**C**) Colocalization of EGFP-labeled PML and various EGFP-labeled PML deletion mutants with ReAsH in HeLa cells. Schematic structures of the deletion mutants are provided in fig. S2A. Scale bar, 10 μm.

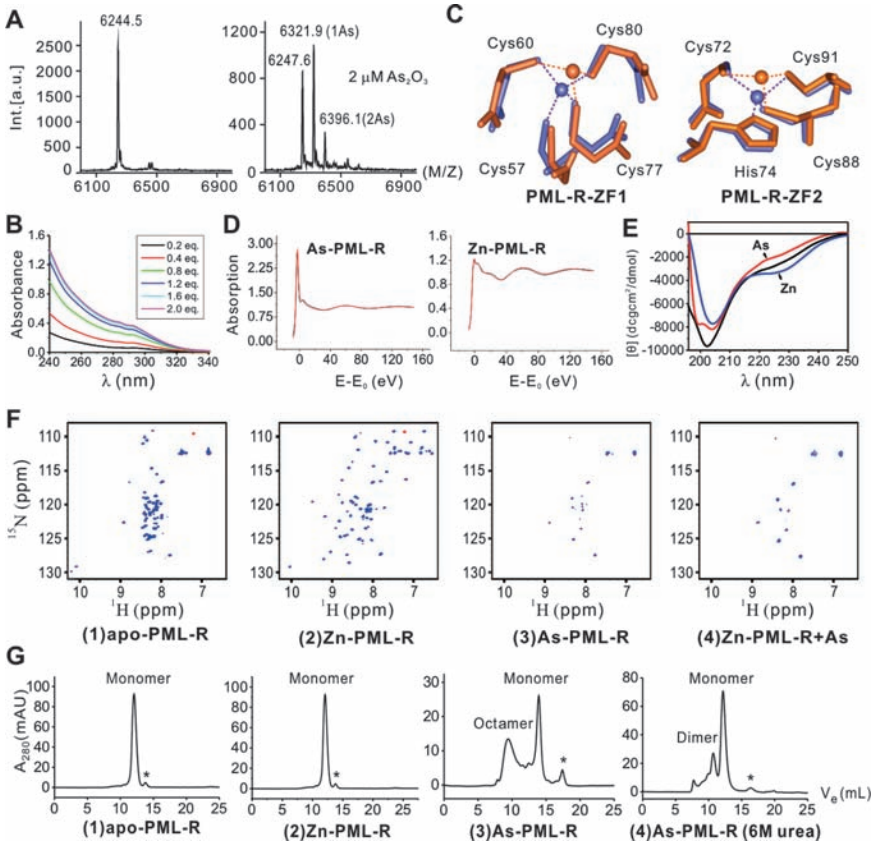

Fig. 3. Arsenic binds to PML-R and induces a conformational change in this protein domain in vitro. (**A**) The interaction between apo-PML-R and arsenic. Apo-PML-R was incubated with As_2O_3 (As-PML-R) and then analyzed by MALDI-TOF mass spectrometry. The numbers shown in parentheses near the peaks represent the number of arsenic atoms bound to the parental peptides. (**B**) Near-ultraviolet absorbance spectrometry assay of apo-PML-R titrated with As_2O_3. (**C**) Local structure showing conserved cysteines and/or histidine around metal ions of Zn-PML-R (orange) or As-PML-R (blue), obtained by XANES and EXAFS analysis. (**D**) XANES spectra. Black curves represent experimental data and red lines, the best fit (*13*). (**E**) CD spectra of apo-PML-R (black line) titrated with $ZnCl_2$ (blue) or As_2O_3 (red). (**F**) NMR HSQC spectra of (1) apo-PML-R, (2) Zn-PML-R, (3) As-PML-R, and (4) Zn-PML-R titrated with 10 eq. of As_2O_3. PML-R in NaAc buffer (pH 5.6) was titrated stepwise with $ZnCl_2$ or As_2O_3 under NMR HSQC monitoring. (**G**) Gel filtration of (1) apo-PML-R, (2) Zn-PML-R, (3) As-PML-R, and (4) As-PML-R in 6M urea buffer. *Impurity.

nuclear single-quantum coherence (HSQC) spectra further demonstrated that As-PML-R tended to oligomerize as indicated by the disappearance of most of its resonance peaks (Fig. 3F, panel 3), different from the well-folded Zn-PML-R (Fig. 3F, panel 2). It was noteworthy that Zn-PML-R oligomerized when excessive As_2O_3 (10 eq.) was added (Fig. 3F, panel 4) and showed an HSQC spectrum similar to that of As-PML-R (Fig. 3F, panel 3). This observation suggests that arsenic might replace the zinc in Zn-PML-R under these conditions.

Gel filtration studies revealed that the PML-R oligomers induced by arsenic binding were primarily octamers (Fig. 3G, panel 3). Under denaturing condition such as 6M urea, a small portion corresponding to homodimers remained, probably because of arsenic-mediated cross-linking between two PML-R molecules (Fig. 3G, panel 4). This hypothesis is consistent with our observations that As_2O_3 promotes PML NBs aggregation in cells (Fig. 1B and fig. S7A) and that these aggregates are resistant to disruption by detergent-containing buffers, such as RIPA and 3M urea buffer (fig. S7B). This resistance could be responsible for the rapid transfer of PML from the supernatant of cell lysates to the pellet after As_2O_3 treatment (fig. S7C). Since transfer of PML to the pellet preceded its appearance as a high-molecular-weight species (Fig. 1C and fig. S7C), it is possible that arsenic-induced oligomerization of PML facilitates the protein's subsequent modification by SUMOylation and ubiquitination and enhances its degradation.

We therefore performed an in vitro SUMOylation assay to investigate whether these posttranslational modifications might be due to structural changes of PML induced by arsenic binding. Note that As_2O_3-pretreatment of PML enhanced its SUMO-2 modification in vitro (Fig. 4A). This

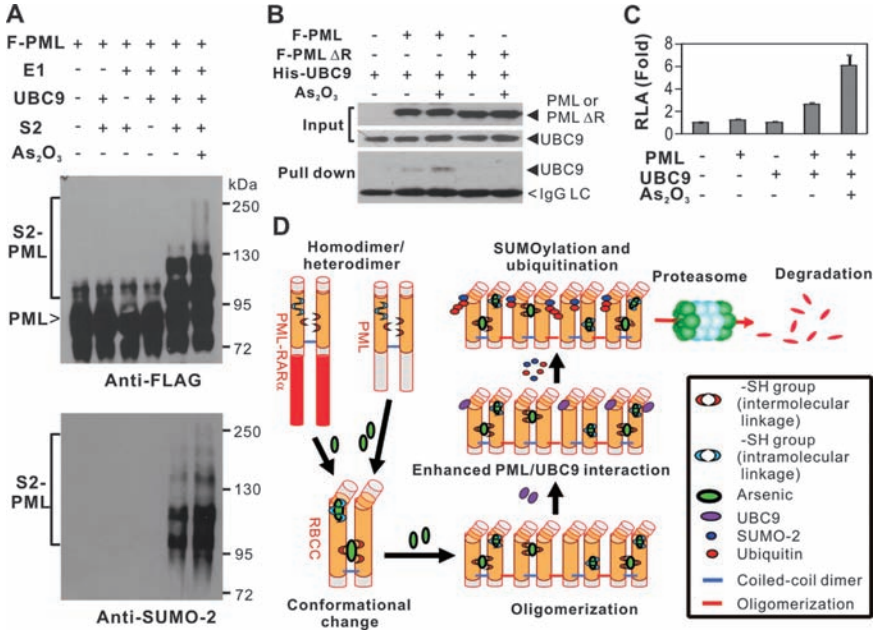

Fig. 4. Biological consequences of the structural change in PML that is induced by arsenic binding. (**A**) Arsenic binding enhances SUMO-2 (S2) modification of PML. For determination of the effect of As_2O_3 on SUMO conjugation, anti-FLAG (FLAG antibody–labeled) M2 beads with FLAG-PML (F-PML) were incubated with As_2O_3 and then stringently washed to remove free arsenic before in vitro SUMOylation. E1: SAE1/SAE2, SUMO activating enzyme. (**B**) Arsenic binding enhances the PML-R-mediated interaction between PML and UBC9 in vitro. (**C**) Arsenic enhances the interaction between PML and UBC9 in HeLa cells. The interaction of PML and UBC9 was determined by mammalian two-hybrid assay. RLA, relative luciferase activity. (**D**) A working model of the mechanism by which As_2O_3 controls the fate of PML and PML-RARα.

was accompanied by an enhanced interaction between PML and UBC9, the E2 SUMO-conjugating enzyme (Fig. 4B); this enhanced interaction also occurred in intact cells, as measured by a mammalian two-hybrid assay (Fig. 4C). The interaction of PML with UBC9 was mediated by PML-R (Fig. 4B), which points to an important role of PML-R in regulating SUMOylation. Predictions from structural modeling indicate that amino acid residues Q58 and Q59 in ZF1 of PML-R could directly contact UBC9 (fig. S8). The conformational change in ZF1 that is induced by arsenic binding might alter the conformation and position of Q58 and/or Q59 and increase the binding affinity of UBC9 for PML-R, which in turn might lead to enhanced SUMOylation of PML-R.

On the basis of our data and previous observations that PML-RARα and PML are capable of homodimerization or heterodimerization through the PML coiled-coil domain (*16*, *17*), we propose the following mechanistic model for arsenic-induced degradation of PML and PML-RARα: Arsenic binds to cysteines in the ZFs of the PML RBCC domains either intramolecularly or by forming cross-links between the two RBCC molecules in the homodimer. The resultant conformational changes may facilitate further oligomerization of PML-RARα or PML and promote SUMOylation of these proteins through enhanced interaction of PML with the enzymes that catalyze this modification (such as UBC9) or through enhanced exposure of the modification sites. Ultimately this would lead to enhanced ubiquitination and degradation of PML and the PML-RARα oncoprotein (Fig. 4D) (*7*, *11*). The structural and molecular basis for the exquisite sensitivity of PML ZFs to arsenic merits further investigation.

In summary, we have demonstrated that arsenic binds directly to the PML-RARα oncoprotein that drives the development of APL. This interaction is likely to explain, at least in part, why As_2O_3 is a clinically effective therapy for patients with APL (*9*, *28*). The identification of PML as a direct target of As_2O_3 opens new perspectives for optimizing the use of this ancient remedy in future leukemia therapies (*29*).

References and Notes

1. Z. Y. Wang, Z. Chen, *Blood* **111**, 2505 (2008).
2. J. Zhu, Z. Chen, V. Lallemand-Breitenbach, H. de Thé, *Nat. Rev. Cancer* **2**, 705 (2002).
3. G. B. Zhou, J. Zhang, Z. Y. Wang, S. J. Chen, Z. Chen, *Philos. Trans. R. Soc. London B Biol. Sci.* **362**, 959 (2007).
4. H. de Thé, C. Chomienne, M. Lanotte, L. Degos, A. Dejean, *Nature* **347**, 558 (1990).
5. Z. X. Shen *et al.*, *Blood* **89**, 3354 (1997).
6. M. E. Huang *et al.*, *Blood* **72**, 567 (1988).
7. J. Zhu *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **94**, 3978 (1997).
8. J. Zhu *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **96**, 14807 (1999).
9. J. Hu *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **106**, 3342 (2009).
10. V. Lallemand-Breitenbach *et al.*, *J. Exp. Med.* **193**, 1361 (2001).
11. V. Lallemand-Breitenbach *et al.*, *Nat. Cell Biol.* **10**, 547 (2008).
12. M. H. Tatham *et al.*, *Nat. Cell Biol.* **10**, 538 (2008).
13. Materials and methods are available as supporting material on *Science* Online.
14. G. Jiang, Z. Gong, X. F. Li, W. R. Cullen, X. C. Le, *Chem. Res. Toxicol.* **16**, 873 (2003).
15. J. Lu, E. H. Chew, A. Holmgren, *Proc. Natl. Acad. Sci. U.S.A.* **104**, 12288 (2007).
16. A. Melnick, J. D. Licht, *Blood* **93**, 3167 (1999).
17. K. Jensen, C. Shiels, P. S. Freemont, *Oncogene* **20**, 7223 (2001).
18. K. L. Borden *et al.*, *EMBO J.* **14**, 1532 (1995).
19. K. L. Borden *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **93**, 1601 (1996).
20. X. Zhang *et al.*, *Cancer Lett.* **255**, 95 (2007).
21. B. R. Martin, B. N. Giepmans, S. R. Adams, R. Y. Tsien, *Nat. Biotechnol.* **23**, 1308 (2005).
22. G. Q. Chen *et al.*, *Blood* **89**, 3345 (1997).
23. E. Duprez *et al.*, *J. Cell Sci.* **112**, 381 (1999).
24. A. M. Spuches, H. G. Kruszyna, A. M. Rich, D. E. Wilcox, *Inorg. Chem.* **44**, 2964 (2005).
25. M. Benfatto, S. Della Longa, C. R. Natoli, *J. Synchrotron Radiat.* **10**, 51 (2003).
26. H. Bhattacharjee, B. P. Rosen, *J. Biol. Chem.* **271**, 24465 (1996).
27. A. M. Spuches, D. E. Wilcox, *J. Am. Chem. Soc.* **130**, 8148 (2008).
28. R. Nasr *et al.*, *Nat. Med.* **14**, 1333 (2008).
29. K. Ito *et al.*, *Nature* **453**, 1072 (2008).

30. We thank E.-D. Wang, K.-K. Wang, J. Zhu, and X.-J. Sun for constructive comments on the work; Y.-Y. Shi, H.-L. Jiang, J.-H. Mao, C.-F. Wu, Y.-Y. Xie, Y.-G. Chang, Y.-J. Jiang, and W.-S. Chu for experimental assistance; X.-D. Xi, N. Kieffer, and J. Zhu for critical reading of the manuscript; and all members of Shanghai Institute of Hematology for their encouragement. This work was supported in part by 863 Program (2006AA02A405), 973 Project (2010CB529201, 2006CB910305), the National Natural Science Foundation of China (30801372, 30623010, 30772744, 30830119, 10734070), the Shanghai Municipal Commission for Science and Technology (07DZ05908 and 08DZ2200100), and the Samuel Waxman Cancer Research Foundation Co-Principal Investigator Program.

Supporting Online Material

www.sciencemag.org/cgi/content/full/328/5975/240/DC1
Materials and Methods
Figs. S1 to S8
Tables S1 and S2
References

16 October 2009; accepted 9 March 2010
10.1126/science.1183424

Transnuclear Mice with Predefined T Cell Receptor Specificities Against *Toxoplasma gondii* Obtained via SCNT

Oktay Kirak,[1]* Eva-Maria Frickel,[1] Gijsbert M. Grotenbreg,[1]† Heikyung Suh,[1] Rudolf Jaenisch,[1,2]* Hidde L. Ploegh[1,2]*

Mice that are transgenic for rearranged antigen-specific T cell receptors (TCRs) are essential tools to study T cell development and function. Such TCRs are usually isolated from the relevant T cells after long-term culture, often after repeated antigen stimulation, which unavoidably skews the T cell population used. Random genomic integration of the TCR α and β chain and expression from nonendogenous promoters represent additional drawbacks of transgenics. Using epigenetic reprogramming via somatic cell nuclear transfer, we demonstrated that T cells with predefined specificities against *Toxoplasma gondii* can be used to generate mouse models that express the TCR from their endogenous loci, without experimentally introduced genetic modification. The relative ease and speed with which such transnuclear models can be obtained holds promise for the construction of other disease models.

The resolution of an infectious disease requires careful orchestration of innate and adaptive immunity. B and T cells specific for infectious agents are not easily obtained in abundant and pure form, yet their availability is crucial in defining their activation requirements and protective properties, either as a single clone or as an ensemble of different specificities. During the peak of an immune response, as many as 30% of all $CD8^+$ T cells may be pathogen-specific (*1*, *2*). For viral pathogens such as vaccinia virus or mouse herpes virus-68, several dozen antigens may be recognized by $CD8^+$ and $CD4^+$ T cells (*3*–*5*). Existing T cell receptor (TCR) transgenic mouse models have all been constructed from T-cell clones or hybridomas selected for survival and response to antigens in vitro. Whether these transgenic mouse models accurately reflect the affinities and activation requirements of lymphocytes triggered during a physiological response to an infection is not known.

Somatic cell nuclear transfer (SCNT) allows the generation of embryonic stem cells (ESCs)

[1]Whitehead Institute for Biomedical Research, Cambridge, MA 02142, USA. [2]Department of Biology, Massachusetts Institute of Technology, Cambridge, MA 02142, USA.

*To whom correspondence should be addressed. E-mail: kirak@wi.mit.edu (O.K.); jaenisch@wi.mit.edu (R.J.); ploegh@wi.mit.edu (H.L.P.).

†Current address: Immunology Programme and Departments of Microbiology and Biological Sciences, National University of Singapore, 117456 Singapore.

ERRATUM

Post date 21 May 2010

Reports: "Arsenic trioxide controls the fate of the PML-RARα oncoprotein by directly binding PML" by X.-W. Zhang *et al*. (9 April, p. 240). In the legend for Fig. 3C, the local structure models were described incorrectly; Zn-PML-R is blue and As-PML-R is orange.