American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
editorial@hematology.org

Identifying *STRN3-RARA* as a new fusion gene for acute promyelocytic leukemia

Tracking no: BLD-2023-020619R2

Qi Zhang (Department of Hematology, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, China) He Li (Department of Hematology, Institute of Hematology, West China Hospital, Sichuan University, China) Xuelan Chen (West China Hospital of Sichuan University, China) Fan Gu (Sichuan University, China) Lanxin Zhang (Sichuan University, China) Lu Zhang (Sichuan University, China) Tong Chen (Sichuan Hua Xi Kindstar Medical Diagnostic Centre, China) Qiang Chen (Sichuan neo-life stem cell biotech inc., Institute of Blood Transfusion, Chinese Academy of Medical Sciences and Peking Union Medical College, China) Wentong Meng (Laboratory of Stem Cell Biology, State Key Laboratory of Biotherapy, West China Hospital, China) Yu Wu (Sichuan University West China Hospital, China) Hong Chang (Department of Hematology, Institute of Hematology, West China Hospital, Sichuan University, , China) Ting Liu (Department of Hematology, Institute of Hematology, West China Hospital of Sichuan University, China) Chong Chen (Department of Hematology, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, China) Hongbing Ma (Department of Hematology, Institute of Hematology, West China Hospital, Sichuan University, China) Yu Liu (Department of Hematology and Institute of Hematology, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, China)

Abstract:
Here we report a new fusion gene, *STRN3-RARA*, in acute promyelocytic leukemia (APL). It cooperates with *UTX* deficiency to drive full-blown APL in mice. While *STRN3-RARA* leukemia quickly relapses after ATRA treatment, they can be restrained by cepharanthine.

Conflict of interest: No COI declared

COI notes:

Preprint server: No;

Author contributions and disclosures: Y.L., H.M. designed and supervised this study; T.L. , C.C. and W.M. were involved in the study design; H.M., H.L., Y.W., and H.C. recruited and treated the patient; Q.Z., F.G., L.Z., and T.C. designed and performed experiments; X.C. and L.Z. performed the bioinformatic analyses; Q.C. provided human cells; Y.L., H.M., C.C., Q.Z. and X.C. analyzed the data and wrote the manuscript.

Non-author contributions and disclosures: No;

Agreement to Share Publication-Related Data and Data Sharing Statement: Emails to the corresponding author and the RNA-seq and CUT&TAG data in this study are deposited in NCBI GEO: GSE224816.

Clinical trial registration information (if any):

Identifying *STRN3-RARA* as a new fusion gene for acute promyelocytic leukemia

Qi Zhang[#,1], He Li[#,2], Xuelan Chen[#,1], Fan Gu[1], Lanxin Zhang[1], Lu Zhang[1], Tong Chen[3], Qiang Chen[4], Wentong Meng[5], Yu Wu[2], Hong Chang[2], Ting Liu[2], Chong Chen[1], Hongbing Ma*[,2], Yu Liu*[,1]

1. Department of Hematology and Institute of Hematology, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China
2. Department of Hematology, Hematology Research Laboratory, West China Hospital, Sichuan University, Chengdu, Sichuan, China
3. Sichuan Hua Xi Kindstar Medical Diagnostic Centre, Chengdu, Sichuan, China
4. Sichuan neo-life stem cell biotech inc., Institute of Blood Transfusion, Chinese Academy of Medical Sciences and Peking Union Medical College, Chengdu, Sichuan, China
5. Laboratory of Stem Cell Biology, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, China.

# Q. Zhang, H. Li, and X. Chen contributed equally to this work.

*Corresponding authors: Hongbing Ma （hongbingma@foxmail.com）, Yu Liu (yuliuscu@scu.edu.cn).

Data Sharing: Emails to the corresponding author and the RNA-seq and CUT&TAG data in this study are deposited in NCBI GEO: GSE224816.

Total of 1200 words for the text. 2 figures and 19 references were listed.

Scientific Category: Myeloid Neoplasia

Abstract

Here we report a new fusion gene, *STRN3-RARA*, in acute promyelocytic leukemia (APL). It cooperates with *UTX* deficiency to drive full-blown APL in mice. While *STRN3-RARA* leukemia quickly relapses after ATRA treatment, they can be restrained by cepharanthine.

TO THE EDITOR:

Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia, that is generally driven by *PML-RARA*, resulting from a balanced chromosomal translocation t(15;17) (q24.1;q21.2)[1,2]. However, approximately 2% of APL patients carry other variants of *RARA*-fusions, which pose challenges for diagnosis and treatment[3,4]. Here, we report a novel t(14;17) translocation in an APL patient that gave rise to a new fusion gene, *STRN3-RARA*. STRN3 forms a complex called the striatin-interacting phosphatase and kinase (STRIPAK), which couples kinases to protein phosphatase 2A and regulates their activities[5]. Like other APL patients with *RARA*-variants, this patient quickly relapsed after the initial response to all-trans retinoic acid (ATRA) treatment[6,7]. Mechanistically, we demonstrated that *STRN3-RARA,* in cooperating with *UTX* deficiency, which was mutated in the patient, drove APL formation in mice. Additionally, we found that *STRN3-RARA* cells were specifically susceptible to the TNFα pathway. Inhibition of this pathway by cepharanthine, an FDA-approved drug, effectively suppressed the growth of U937 cells with *STRN3-RARA* expression, as well as relapsed APL cells from the patient. Taken together, our study identified a new APL fusion gene, *STRN3-RARA*, and validated it as a functional APL driver, providing insight into the diagnosis and treatment of non-classic APL patients.

A 50-year-old male patient (WCH01) was admitted to the hospital with leukopenia and coagulopathy. In the bone marrow (BM), 91.5% of cells were hypergranular promyelocytes (Figure 1A), combined with immunophenotype and other clinicopathological features, this WCH01 patient was diagnosed with APL (Figure 1B and Supplemental Table 1). Further transcriptomic analysis of WCH01 showed enrichment of gene signatures of APL_PML_RARA[8] (Figure 1C). However, the classic chromosome translocation t(15;17) was not detected using the fluorescence in situ hybridization (FISH) test with *PML* and *RARA* probes (Supplemental Figure 1A). Instead, a new translocation between chromosomes 14 and 17 was found in the karyotyping result, which was further confirmed by RNA sequencing (RNA-seq) and Sanger sequencing (Figure 1D-F). This fusion happened between *STRN3* exon 3 and *RARA* exon 3, resulting in a new *STRN3-RARA* fusion. Additionally, several gene mutations, including *UTX* frameshift mutation, were detected by the RNA-seq of WCH01 APL cells (Figure 1G and Supplemental Figure 1B).

Initially, the WCH01 patient achieved complete remission with standard ATRA and arsenic trioxide (ATO) combination treatment, followed by consolidation with anthracycline-based therapy and maintenance with ATRA and arsenic trioxide. But after 10 months, he quickly relapsed and became resistant to ATRA and ATO treatment (Figure 1H and Supplemental Figure 1C-E). A novel RARA missense mutation (S232F) was detected in the relapse sample (Supplemental Figure 1F). The WCH01 patient then received a combination of ATRA and venetoclax. But unfortunately, no response was found either. He quickly developed severe pneumonia and eventually died from respiratory failure after 14 days of treatment with ATRA and venetoclax (Figure 1H).

To investigate the role of the *STRN3-RARA* (*SR*) fusion, we cloned Flag-tagged *SR* cDNA into a GFP-expressing retrovirus-based construct (*pMSCV-Flag-SR-IRES-GFP*) and transduced it into cell lines. Like PML-RARA and other reported RARA variant fusion proteins, the SR protein was predominantly located in the nucleus and was sensitive to ATRA treatment[9,10] (Figure 2A-B and Supplemental Figure 2A). Transcriptomics analysis of U937 cells with *SR* showed that APL_PML_RARA-upregulated genes were significantly positively enriched in *SR* cells (Figure 2C), which was consistent with the significant overlap of the differentially expressed genes in *PML-RARA* and those in *STRN3-RARA* (Supplemental Figure 2B-C). We further conducted CUT&Tag sequencing of *Flag-SR* U937 cells to discover the SR-binding sites (Figure 2D) and found that these SR-binding sites significantly overlapped with PML-RARA-binding genes[11] (Figure 2E). Combined with RNA-seq data, we found that SR protein directly bound to genes and upregulated many APL-related genes or downregulated multiple differentiation-related genes (Supplemental Figure 2B-E). These results suggest that, like PML-RARA, the STRN3-RARA oncogenic protein exerts both repressive and activating functions through direct binding[11].

To investigate the role of *SR* in APL genesis, we transduced the hematopoietic stem and progenitor cells (HSPCs) with *SR* and followed by transplantation into sub-lethal irradiated recipient mice. We found that *SR* alone was insufficient to induce a full-blown APL in mice over a 5-month period, which is consistent with the previous observations in the *PML-RARA* mouse model[12] (Supplemental Figure 3). Considering that the frameshift mutation of a known tumor suppressor gene *UTX* was detected[13,14,15,16] (Figure 1G), we investigated the role of *SR* in murine APL formation with *Utx* sgRNA (sg*Utx*). The results showed that all sg*Utx*;*SR* cohort mice had developed leukemia 175 days after transplantation while none of the sg*Utx*;Vector control mice were sick (Figure 2F and Supplementary Figure 4A-H). The peripheral blood smear results displayed blast cells with abnormal promyelocytic morphology (Figure 2G). Pathological examinations of the BM, spleen, and liver also revealed the infiltration of leukemic cells (Supplemental Figure 4I-K). Besides, recipient mice transplanted with sg*Utx;SR* APL cells received ATRA or vehicle treatment, resulting in a reduction of GFP+mCherry+ APL cells in the peripheral blood. The induction of differentiation was observed through blood smear and RNA-seq analysis (Figure 2H-I and Supplementary Figure 5). Furthermore, the treatment significantly extended the survival of the recipient mice (Figure 2J). These results indicate that *SR* fusion with *Utx* deficiency drives APL.

To elucidate the molecular mechanisms underlying the cooperation between *SR* fusion and *UTX* loss, we compared the gene expression upregulated or downregulated in the WCH01 compared to normal human bone marrow cells or in U937 cells with *sgUTX;SR* compared to that with empty vector and found that 454 upregulated genes (common_up_454) and 587 downregulated genes (common_down_587) were significantly overlapped[17,18] (Supplemental Figure 6A-C). According to these gene expression patterns, we divided the common_up_454 genes (or common_down_587) into three groups and labeled them with different colors. Genes in the green group were likely regulated mainly by *SR*, Genes in the orange group were regulated mainly by *UTX*, and genes in the blue group seem to be under the control of both *UTX* and *SR* (Supplemental Figure 6D-E).

To find a new inhibitor for sg*UTX;SR*, we searched for candidate drug targetable genes that specifically upregulated by *sgUTX;SR* but not *PML-RARA*, *TNF* gene and pathway were at the top of the list (Figure 2K-L). Therefore, we examined the impact of TNFα inhibitor cepharanthine, an FDA-approved drug, on the growth of U937 cells with vector, sg*UTX*, *SR*, or sg*UTX*;*SR*[19]. Our results demonstrated that U937 cells with *SR* or sg*UTX*;*SR* was more sensitive to cepharanthine than control cells (Figure 2M). Furthermore, while clinical *SR* APL cells collected from relapsed WCH01 patient showed no response to ATRA treatment, their viability was reduced by cepharanthine treatment (Figure 2N). These results suggest that cepharanthine could serve as a potential therapeutic method for APL patients with *STRN3-RARA* fusion.

In conclusion, we have identified a novel fusion gene, *STRN3-RARA*, in a patient with APL. This *SR* APL displayed similar clinical and pathological characteristics as classical APL patients carrying *PML-RARA*. Additionally, we have demonstrated that *SR*, with the *Utx* loss, drove APL genesis in mice, revealing the oncogenic role of this fusion gene in leukemogenesis. Furthermore, we found that *SR* APL cells collected from relapsed WCH01 patient were sensitive to the inhibitor of TNFα signaling pathway. Taken together, our findings not only advance the understanding of APL disease but also provide valuable insights for the diagnosis and treatment of patients with APL variants.

Informed consent was obtained from the patient's family. All mouse experiments were approved by the Institutional Animal Care and Use Committee of of West China Hospital of Sichuan University.

Acknowledgments

We thank the WCH01 patient and his family. We thank all the members of the Chen and Liu laboratory for their technical support and suggestions. We thank Dr. Yuquan Wei for his generous support. We thank Zhihong Xu and Ying Lin at Sichuan Hua Xi Kindstar Medical Diagnostic Centre for their valuable assistance with karyotype and FISH analysis. We thank Qiaorong Huang at the Laboratory of Stem Cell Biology, West China Hospital, Sichuan University for assistance with flow cytometry analysis. We thank the Core Facilities of West China Hospital for technical support. This work was supported by the National Natural Science Foundation of China (82130007, Y.L.; 81670182, Y.L.; 82170171, C.C.; 81770157, C.C.), the China Postdoctoral Science Foundation (2023M732465, Q.Z.; 2023M732434, X.C.), the Sichuan Science and Technology Program (2020YFQ0059, C.C.; 2018JZ0077, Y.L.; 2020ZYD002, Y.L. and 2017TJPT0005, C.C.), the 1.3.5. Project for Disciplines of Excellence, West China Hospital, Sichuan University (ZYGD22012, Y.L.; ZYJC21009, Y.L.; 2022HXFH040, H.M. and ZYYC20004, C.C.), the Post-Doctor Research Project, West China Hospital, Sichuan University (2023HXBH094, Q.Z.; 2023HXBH033, X.C.) and the Sichuan University Postdoctoral Interdisciplinary Innovation Fund (JCXK2210, X.C.).

Authorship Contributions

Y.L., H.M. designed and supervised this study; T.L. , C.C. and W.M. were involved in the study design; H.M., H.L., Y.W., and H.C. recruited and treated the patient; Q.Z., F.G., L.Z., and T.C. designed and performed experiments; X.C. and L.Z. performed the bioinformatic analyses; Q.C. provided human cells; Y.L., H.M., C.C., Q.Z. and X.C. analyzed the data and wrote the manuscript.

Disclosure of Conflicts of Interest

The authors declare no competing financial interest.

References

1. Hugues de The, Christine Chomiennet MLDD. The t(15;17) translocation of acute promyelocytic leukaemia fuses the retinoic acid receptor α gene to a novel transcribed locus. *Nature*. 1990;347(October):558-561.
2. Wang Z-Y, Chen Z. Acute promyelocytic leukemia: from highly fatal to highly curable. *Blood, J Am Soc Hematol*. 2008;111(5):2505-2515.
3. Grimwade D, Biondi A, Mozziconacci MJ, et al. Characterization of acute promyelocytic leukemia cases lacking the classic t(15;17): Results of the

European Working Party. *Blood*. 2000;96(4):1297-1308. doi:10.1182/blood.V96.4.1297

4. Wen L, Xu Y, Yao L, et al. Clinical and molecular features of acute promyelocytic leukemia with variant retinoid acid receptor fusions. *Haematologica*. 2019;104(5):e195.
5. Goudreault M, D'Ambrosio LM, Kean MJ, et al. A PP2A phosphatase high density interaction network identifies a novel striatin-interacting phosphatase and kinase complex linked to the cerebral cavernous malformation 3 (CCM3) protein. *Mol Cell Proteomics*. 2009;8(1):157-171.
6. Zhang X, Sun J, Yu W, Jin J. Current views on the genetic landscape and management of variant acute promyelocytic leukemia. *Biomark Res*. 2021;9(33):1-15. doi:10.1186/s40364-021-00284-x
7. Yamamoto Y, Tsuzuki S, Tsuzuki M, Handa K, Inaguma Y, Emi N. BCOR as a novel fusion partner of retinoic acid receptor alpha in a t (X ; 17)(p11 ; q12) variant of acute promyelocytic leukemia. *Blood*. 2010;116(20):4274-4283. doi:10.1182/blood-2010-01-264432.The
8. Ross ME, Mahfouz R, Onciu M, et al. Gene expression profiling of pediatric acute myelogenous leukemia. *Blood*. 2004;104(12):3679-3687.
9. Noguera NI, Catalano G, Banella C, et al. Acute Promyelocytic Leukemia : Update on the Mechanisms of Leukemogenesis , Resistance and on Innovative Treatment Strategies. *Cancers (Basel)*. 2019;11(1591):1-21.
10. Fischer K, Al-Sawaf O, Fink AM, et al. FNDC3B is another novel partner fused to RARA in the t(3;17)(q26;q21) variant of acute promyelocytic leukemia. *Blood*. 2017;129(19):2702-2705. doi:10.1182/blood-2017-01-761973
11. Tan Y, Wang X, Song H, et al. A PML/RARα direct target atlas redefines transcriptional deregulation in acute promyelocytic leukemia. *Blood*. 2021;137(11):1503-1516.
12. Grisolano JL, Wesselschmidt RL, Pelicci PG, Ley TJ. Altered myeloid development and acute leukemia in transgenic mice expressing PML-RARα under control of cathepsin G regulatory sequences. *Blood, J Am Soc Hematol*. 1997;89(2):376-387.
13. Wang L, Shilatifard A. UTX Mutations in Human Cancer. *Cancer Cell*. 2019;35(2):168-176. doi:10.1016/j.ccell.2019.01.001
14. Gozdecka M, Meduri E, Mazan M, et al. UTX-mediated enhancer and chromatin remodeling suppresses myeloid leukemogenesis through noncatalytic inverse regulation of ETS and GATA programs. *Nat Genet*. 2018;50(6):883-894.
15. Stief SM, Hanneforth A-L, Weser S, et al. Loss of KDM6A confers drug resistance in acute myeloid leukemia. *Leukemia*. 2020;34(1):50-62.
16. Wartman LD, Larson DE, Xiang Z, et al. Sequencing a mouse acute promyelocytic leukemia genome reveals genetic events relevant for disease progression. *J Clin Invest*. 2011;121(4):1445-1455. doi:10.1172/JCI45284
17. Payton JE, Grieselhuber NR, Chang L-W, et al. High throughput digital

quantification of mRNA abundance in primary human acute myeloid leukemia samples. *J Clin Invest*. 2009;119(6):1714-1726.

18. de Jonge HJM, Valk PJM, Veeger NJGM, et al. High VEGFC expression is associated with unique gene expression profiles and predicts adverse prognosis in pediatric and adult acute myeloid leukemia. *Blood, J Am Soc Hematol*. 2010;116(10):1747-1754.
19. Bailly C. Cepharanthine: An update of its mode of action, pharmacological properties and medical applications. *Phytomedicine*. 2019;62(March):152956. doi:10.1016/j.phymed.2019.152956

Figure legends

Figure 1. Identifying an APL with *STRN3-RARA* translocation.

(A) Bone marrow (BM) smear of the WCH01 patient before treatment. Scale bar, 10 μm.

(B) Flow cytometry analysis of the WCH01 patient's BM cells before treatment. The expression of CD13, CD33, CD117, CD34 and HLA-DR is shown. The numbers indicate the percentage of different cell populations.

(C) Gene Set Enrichment Analysis (GSEA) showing the positive enrichment of the APL_PML_RARA gene set in the WCH01 patient, comparing to normal ones (NES=2.47; *p*-value=0.00).

(D) Cytogenetics analysis of the WCH01 patient's BM cells before treatment. The karyotype analysis of the WCH01 patient reveals the following abnormalities: 45, XY, add(6)(q13), der(14)t(14,17)(q12;q21) dup(17)(q21q25), -16, -17, add(18)(p11), der(19)t(15;19)(q22;p13.3), add(21)(p11), +mar, inc[20]. Red arrows highlight the t(14,17) chromosome translocation.

(E) The circular plot showing an overview of the top 10 fusion events between locations in chromosomes.

(F) Schematic representation and Sanger sequencing of the *STRN3-RARA* fusion. The yellow blocks represent exons of the *STRN3* gene (NM_014574.3), and the green blocks represent exons of the *RARA* gene (NM_000964.3). Numbers in the blocks indicate the exon number. The Sanger sequencing at the breakpoint site is shown at the bottom.

(G) Sanger sequencing of the *UTX* locus obtained from the PCR product of the WCH01 patient.

(H) Percentage of blast cells in the WCH01 patient's bone marrow during treatment. The blocks indicate the drug treatments administered during the period. ATRA, all-trans retinoic acid; ATO, arsenic trioxide; DA, daunorubicin and cytarabine; HA, homoharringtonine and cytarabine; Ven, venetoclax.

Figure 2. The oncogenic role of *STRN3-RARA* fusion gene in leukemogenesis.

(A) Treatment curve of U937 cells with ATRA and ATO. Cells were transduced with vector or *STRN3-RARA*. Showing as means ± SD, n=3. **p*<0.05, ***p*<0.01, *****p*<0.0001 (Two-way ANOVO).

(B) Western blot analysis of ATRA-treated 293T cells harvested 2 days after treatment. 293T cells were transduced with *Flag-STRN3-RARA*.

(C) GSEA showing positive enrichment of the APL_PML_RARA gene set in U937 cell with *STRN3-RARA* overexpression, comparing to vector (NES=1.57; *p*-value=0.01).

(D) Levels of STRN3-RARA bound at the transcription start site (TSS) in U937 cells transduced with *STRN3-RARA*, measured by the CUT&Tag analysis.

(E) The Venn diagram showing the overlap of binding-genes in STRN3-RARA and PML-RARA (hypergeometric test).

(F) Kaplan-Meier tumor-free survival curves of recipient mice in vector and *STRN3-RARA* group with *Utx* knockout, n=6 (vector), n=8 (*STRN3-RARA*). ***p*<0.01 (Log-rank test).

(G) Blood smear of sg*Utx*;*SR* recipient mouse before sacrificed. Scale bar,10μm.

(H) The percentage of sg*Utx;SR* (GFP+mCherry+) cells along with vehicle and ATRA treatment. The X-axis indicates the number of days after treatment. Showing as means ± SD, vehicle, n=5,4,4,2; ATRA, n=5;4;4;4; *****p*<0.0001 (Two-way ANOVO).

(I) Blood smears from sg*Utx*;*SR* mice following a 25-day treatment with vehicle or ATRA. Scale bar,10μm.

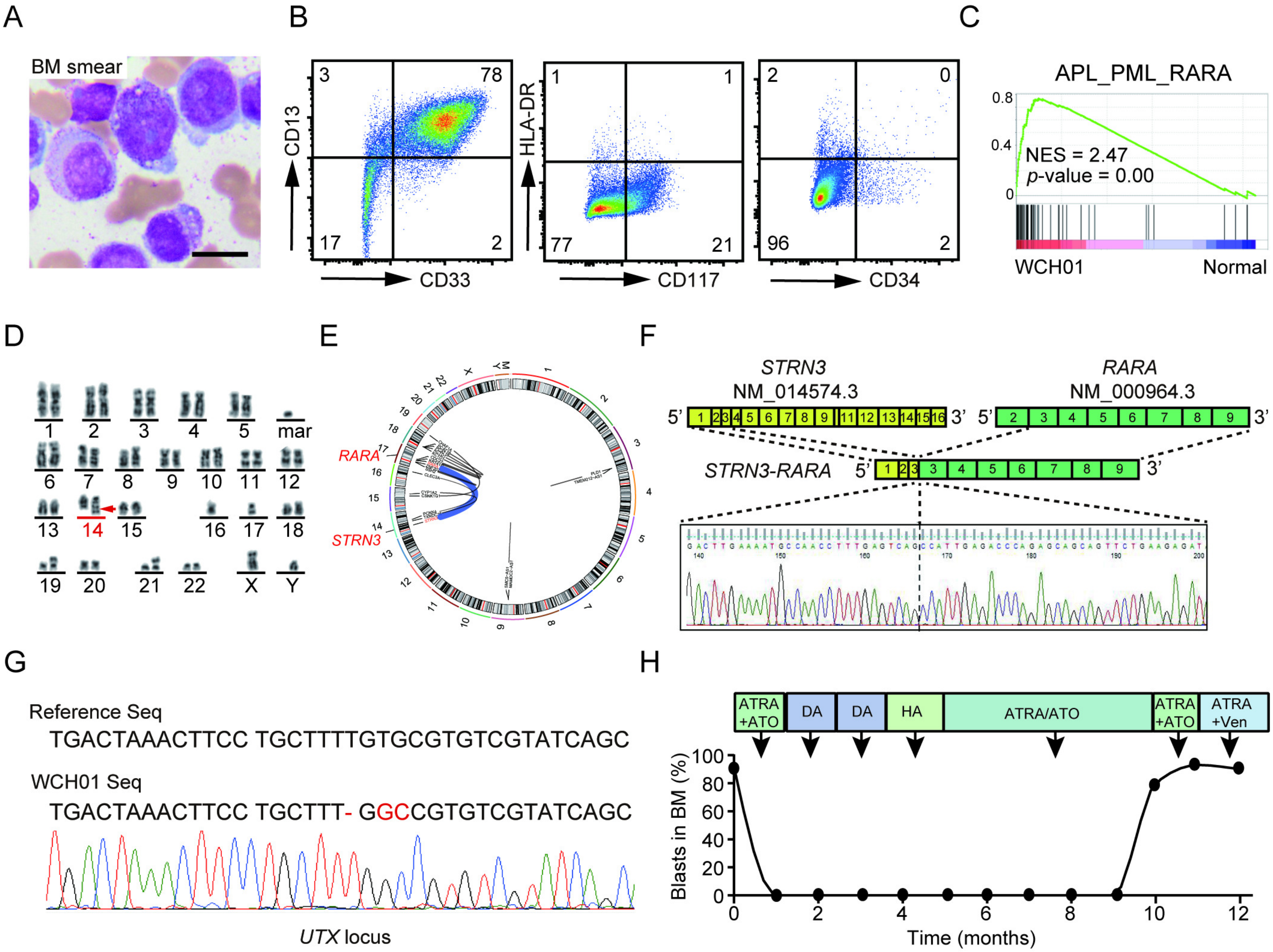
(J) Survival curve of sg*Utx;SR* mice following a 25-day ATRA or vehicle treatment. n=5; **p*<0.05 (Log-rank test).

(K) Heatmap showing the 140 drug targetable genes that were specifically upre gulated in U937 cells with *sgUTX;SR* compared to that with empty vectors, and not overlapped with the upregulated genes due to *PML-RARA*.

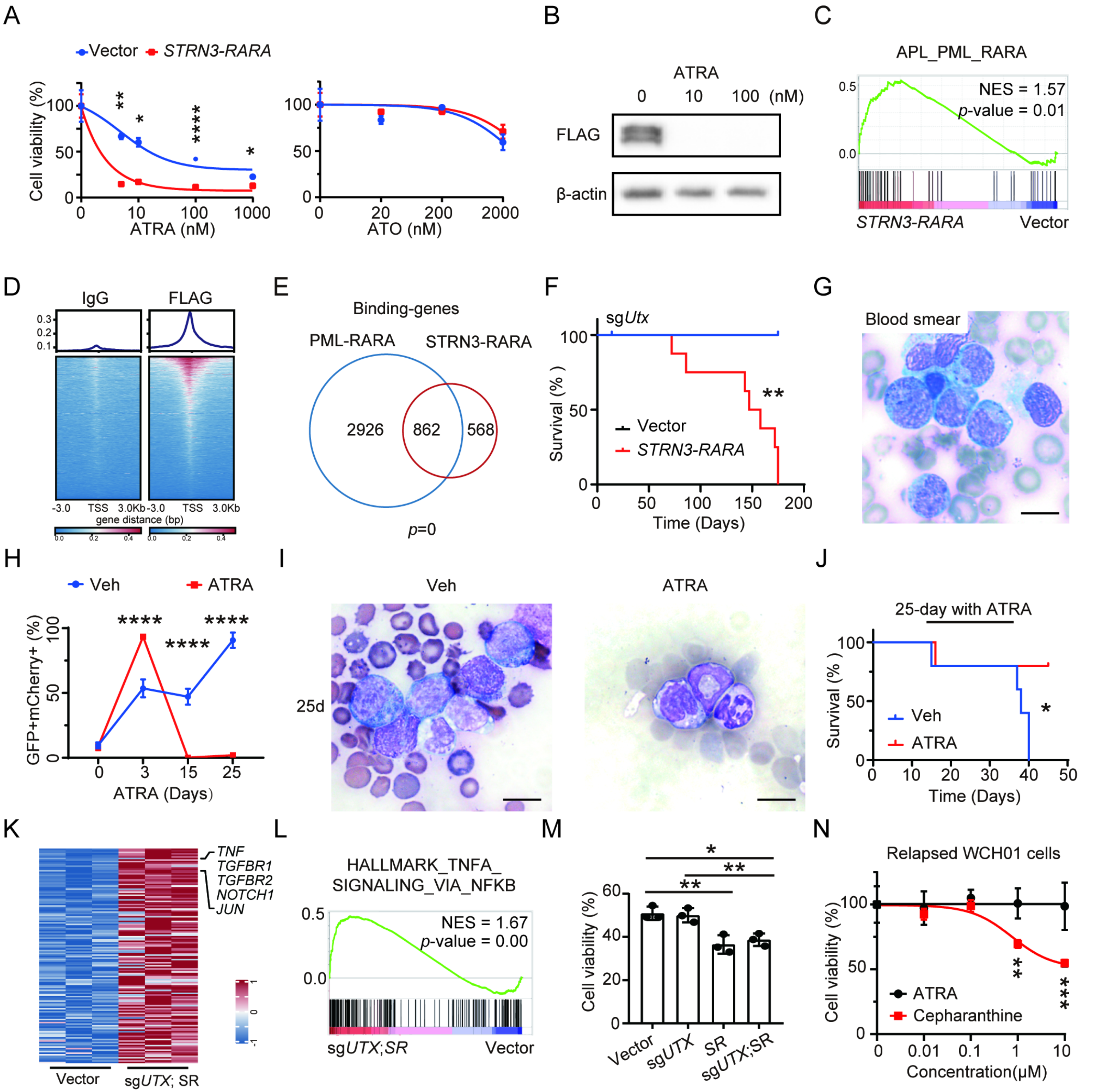
(L) GSEA showing the positive enrichment of the HALLMARK_TNFA_SIGNA LING_VIA_NFKB gene set in sg*UTX*;*SR* U937 cells, comparing to vector (NES=1.67; *p*-value=0.00).

(M) Relative viability of U937 cells treated with 1 μM cepharanthine. Vector, sg*UTX*，*SR*, and sg*UTX*;*SR* groups were shown. Showing as means ± SD, n=3, **p*<0.05, ***p*<0.01 (One-way ANOVA).

(N) Drug treatment survival curve of WCH01 relapsed cells. ATRA and cepharanthine were treated respectively. Showing as means ± SD, n=3, ***p*<0.01, ****p*<0.001 (Two-way ANOVA).



A
BM smear
B
CD13
CD33
HLA-DR
CD117
CD34
C
APL_PML_RARA
NES = 2.47
p-value = 0.00
WCH01
Normal
D
mar
E
RARA
STRN3
F
STRN3
NM_014574.3
RARA
NM_000964.3
STRN3-RARA
G
Reference Seq
TGACTAAACTTCC TGCTTTTGTGCGTGTCGTATCAGC
WCH01 Seq
TGACTAAACTTCC TGCTTT- GGCCGTGTCGTATCAGC
UTX locus
H
ATRA +ATO
DA
DA
HA
ATRA/ATO
ATRA +ATO
ATRA +Ven
Blasts in BM (%)
Time (months)



A
Vector
STRN3-RARA
Cell viability (%)
ATRA (nM)
ATO (nM)
B
ATRA
0 10 100 (nM)
FLAG
β-actin
C
APL_PML_RARA
NES = 1.57
p-value = 0.01
STRN3-RARA
Vector
D
IgG
FLAG
-3.0 TSS 3.0Kb
gene distance (bp)
E
Binding-genes
PML-RARA
STRN3-RARA
2926
862
568
p=0
F
sgUtx
Vector
STRN3-RARA
Survival (%)
Time (Days)
G
Blood smear
H
Veh
ATRA
GFP+mCherry+ (%)
ATRA (Days)
I
Veh
ATRA
25d
J
25-day with ATRA
Veh
ATRA
Survival (%)
Time (Days)
K
TNF
TGFBR1
TGFBR2
NOTCH1
JUN
Vector
sgUTX; SR
L
HALLMARK_TNFA_
SIGNALING_VIA_NFKB
NES = 1.67
p-value = 0.00
sgUTX;SR
Vector
M
Cell viability (%)
Vector
sgUTX
SR
sgUTX;SR
N
Relapsed WCH01 cells
ATRA
Cepharanthine
Cell viability (%)
Concentration(μM)