Supplemental data

Supplemental Figures and Legends

**Supplemental Figure 1.** WDR4 functions as a substrate adaptor of CRL4 to promote PML ubiquitination. (A, B) Immunoprecipitation analysis for PML-I ubiquitination in 293T cells transfected with indicated siRNAs or stably expressing indicated shRNAs. The relative amounts of PML-I ubiquitination is indicated in (A). The knockdown
efficiency of each DCAF shRNA was assayed by RT/qPCR analysis and shown in (B). Data are mean ± SD, n=3 per group, **p<0.01, ***p<0.001, two-tailed Student’s t test. (C) Alignment of the sequence of WDR4 amino acid 204 to 219 with the consensus sequence of DWD box. WDxR motif is indicated. (D) Ni-NTA pull down analysis for WDR4 ubiquitination in 293T cells transfected with indicated constructs. (E) Ni-NTA pull down analysis for PML-I ubiquitination in 293T cells transfected with indicated constructs. (F) Immunoprecipitation analysis of the interaction between WDR4 and PML-I in transfected 293T cells. Asterisk marks a nonspecific band.
Supplemental Figure 2. Identification of the region in WDR4 responsible for PML binding, ubiquitination, and degradation. (A) Predicted structure of WD40-repeat domain of WDR4, based on the yeast Trm82 crystal structure (PDB Accession Code 2VDU). Residues that are deleted in each mutant are in red whereas other loop residues are in green. The R219 residue is marked by a green ball. (B) Amino acid
sequences of WDR4. Residues outside of the predicted structure are in gray. Residues in the \( \beta \)-sheet and loop are in black and red, respectively. Deleted residues are highlighted in yellow. The deletion mutants are named in order from N- to C-terminus as dTL1 to dTL14. (C) In vitro pull down analysis of WDR4 mutants bound on Myc-beads with baculovirally purified PML-I. The relative amounts of bound PML-I are indicated. (D) Immunoprecipitation analysis of PML-I ubiquitination in 293T cells transfected with indicated constructs. (E) Western blot analysis of endogenous PML in H1299 cells transfected with indicated constructs.
Supplemental Figure 3. WDR4 expression and its prognostic value in lung cancer. (A)

Summary of the IHC data of WDR4 expression in various malignant and benign
tumors. (B) WDR4 mRNA expression profiles in non-tumor (N) and tumor (T) lung
tissues (B) revealed from indicated GEO data set. Data are mean ± SD, n=20 for (N),
n=226 for (T), ***p<0.001, two-tailed Student’s t test. (C) Kaplan-Meier analysis of
lung cancer patient survival with WDR4 mRNA expression profiles. Data were retrieved from indicated GEO data set. High and low expression was defined using the median expression level as a cut point. $P$-value is determined by log-rank test.
Supplemental Figure 4. WDR4/PML axis induces a number of tumor-promoting genes. (A) Western blot analysis for WDR4 and PML expression in A549 cells transfected with WDR4 construct or PML siRNA. (B) RT-qPCR analysis of the expression of indicated genes in A549 cells as in (A). Data are mean ± SD, n=3 per group, ***p<0.001, two-tailed Student’s t test. (C) Western blot analysis of indicated
proteins in A549 (left) or H1299 (right) cells transfected with indicated constructs.

(D) Western blot analysis of indicated proteins in CL152 cells stably expressing indicated shRNAs. (E) Expression profiles for NT5E and SAA2 mRNA in lung adenocarcinoma tissues and adjacent normal tissues derived from TCGA data set. P-values are determined by one-way ANOVA with Tukey’s post test. (F) Kaplan-Meier analysis of lung adenocarcinoma patient survival with the corresponding expression profiles derived from TCGA data set. High and low expression was defined using an optimized cut point. (G) Kaplan-Meier analysis of lung cancer patient survival with the corresponding expression profiles. Data were retrieved from indicated GEO data set. High and low expression was defined using the median expression level as a cut point. P-values in (F) and (G) are determined by log-rank test. (H) Western blot analysis of SAA2 in the CM of H1299 cells stably expressing control or HIF-1α shRNA and cultured in hypoxia or normoxia conditions for 24 hr. The knockdown efficiency of HIF-1α shRNA is shown in Figure 4F.
Supplemental Figure 5. WDR4/PML axis promotes lung cancer cell migration and invasion. (A) Western blot analysis of H1299 cells stably expressing WDR4 shRNA and/or PML siRNA. (B) Migration and invasion activities of cells shown in (A). (C) Migration and invasion assays of CL152 cells stably expressing indicated shRNAs. The expression levels of WDR4 and PML in these stable cells are shown in Supplemental Figure 4D. (D) Western blot analysis of CL141 cells stably expressing indicated shRNAs. (E) Migration and invasion assays of cells shown in (D). (F) Western blot analysis of H1299 cells stably expressing WDR4 and/or PML-IV. (G) Migration and invasion activities of cells shown in (F). (H) Migration and invasion activities of A549 cells stably expressing PML shRNA and transfected with indicated siRNAs. (I) Migration and invasion activities of parental H1299 cells treated with CM.
derived from cells as in (A). Data shown in (B), (C), (E), (G), (H) and (I) are mean ± SD, n=3 per group, **p<0.01, ***p<0.001, one-way ANOVA with Tukey’s post test.
Supplemental Figure 6. WDR4/PML axis promotes lung cancer metastasis. (A)

Bioluminescence analysis of lung metastasis derived from indicated A549 cells
(established in Figure 5E). Representative images at week 10 (left) and kinetics of metastasis at indicated time points (right) are shown. Data are mean ± SD, n=8 per group, ***p<0.001 for week 10 data, one-way ANOVA with Tukey’s post test. (B) Lung metastasis and histological analysis of the lung at week 10. Nodules are indicated by arrows. Bars, 2 mm (top) and 500 μm (bottom). (C) Number of metastatic nodules at the surface of lung at week 10. Data are mean ± SD, n=8 per group, ***p<0.001, one-way ANOVA with Tukey’s post test. (D) Bioluminescence analysis of lung metastasis derived from indicated CL152 cells (established in Supplemental Figure 4D). Representative images at week 6 (left) and kinetics of metastasis at indicated time points (right) are shown. Data are mean ± SD, n=5 per group, *p<0.05, **p<0.01, ***p<0.001 for week 6 data, one-way ANOVA with Tukey’s post test. (E) Lung metastasis and histological analysis of the lung at week 6. Nodules are indicated by arrows. Bars, 2 mm (top) and 500 μm (bottom). (F) Number of metastatic nodules at the surface of lung at week 6. Data are mean ± SD, n=5 per group, ***p<0.001, one-way ANOVA with Tukey’s post test.
Supplemental Figure 7. The roles of WDR4/PML axis in regulating downstream effectors and intratumoral immune cells in a syngeneic mouse model. (A) IHC staining for the expression of CD73, uPAR, and SAA2 in primary tumors derived from indicated LLC1 xenografts. Bar, 50 μm. (B, C, D) IHC analyses of CD4, NK1.1, and CD68 using primary tumors at the time of harvest. Quantitative data are shown on the top and representative images are on the bottom. Cells stained positive are indicated by arrows. Data are mean ± SD, n=4 per group, *p<0.05, **p<0.01, one-
way ANOVA with Tukey’s post test. Bar, 50 μm. (E) Representative flow cytometry data for CD4⁺Foxp3⁺ Tregs, CD8⁺ T cells, and CD68⁺CD206⁺ M2-like macrophages in the primary tumors generated by inoculating LLC1 derivatives in syngeneic mice. In all experiments, cells were first gated on CD45⁺ population and then on CD4⁺ population (top) or CD68⁺ population (bottom).
Supplemental Figure 8. Lung tumorigenesis and intratumoral immune cells in KP and KPW mice. (A) Western blot analysis of the expression of indicated proteins in lung
tumors derived from KP and KPW mice. (B) Histological lung sections of KP and KPW mice at 8 and 12 weeks after Ad-Cre administration. Bar, 2 mm. (C, E) Representative images for IHC data of Ki67, Foxp3, CD8, CD206 and Arg-1 in the lung tumors of KP and KPW mice at 8 weeks after tumor induction. Bar, 50 μm. (D) Numbers of hyperplastic lesions, adenomas and adenocarcinomas in KP and KPW mice at 8 weeks after Ad-Cre administration. Data are mean ± SD, n=5 per group. (F) Mediastinal lymph nodes were isolated from KP and KPW mice at 8 weeks after Ad-Cre administration and analyzed for Tregs by flow cytometry as in Figure 9F. The percentages of Foxp3+ cells among CD4+ T cells and CD4+Foxp3+ cells among total analyzed lung cells are quantified. Data are mean ± SD, n=11, two-tailed Student’s t test. (G) Histological lung sections of APCP-treated or untreated KP and KPW mice at 8 weeks after Ad-Cre administration. Bar, 2 mm. (H, I) Representative images for IHC data of Ki67, Foxp3, CD8, CD206 and Arg-1 in lung tumors of APCP-treated KP and KPW mice at 8 weeks after tumor induction. Bar, 50 μm.
### Supplemental Tables

#### Supplemental Table 1: Information for antibodies used in this study

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Supplemental Table 2: Primers for quantitative PCR and mouse genotyping

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19
## Supplemental Table 3: Targeting sequences for siRNAs and shRNAs

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# Supplemental Table 4: Clinical pathological characteristics of lung cancer patients

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***p<0.001, Fisher’s exact test