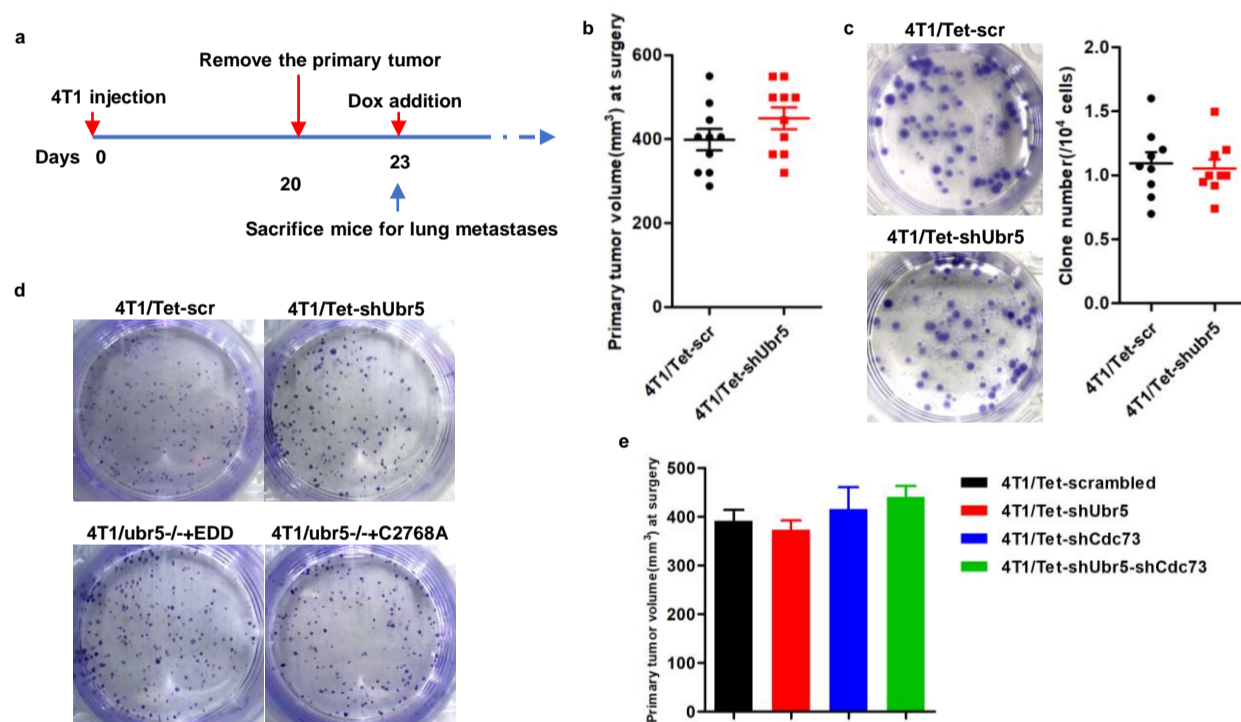
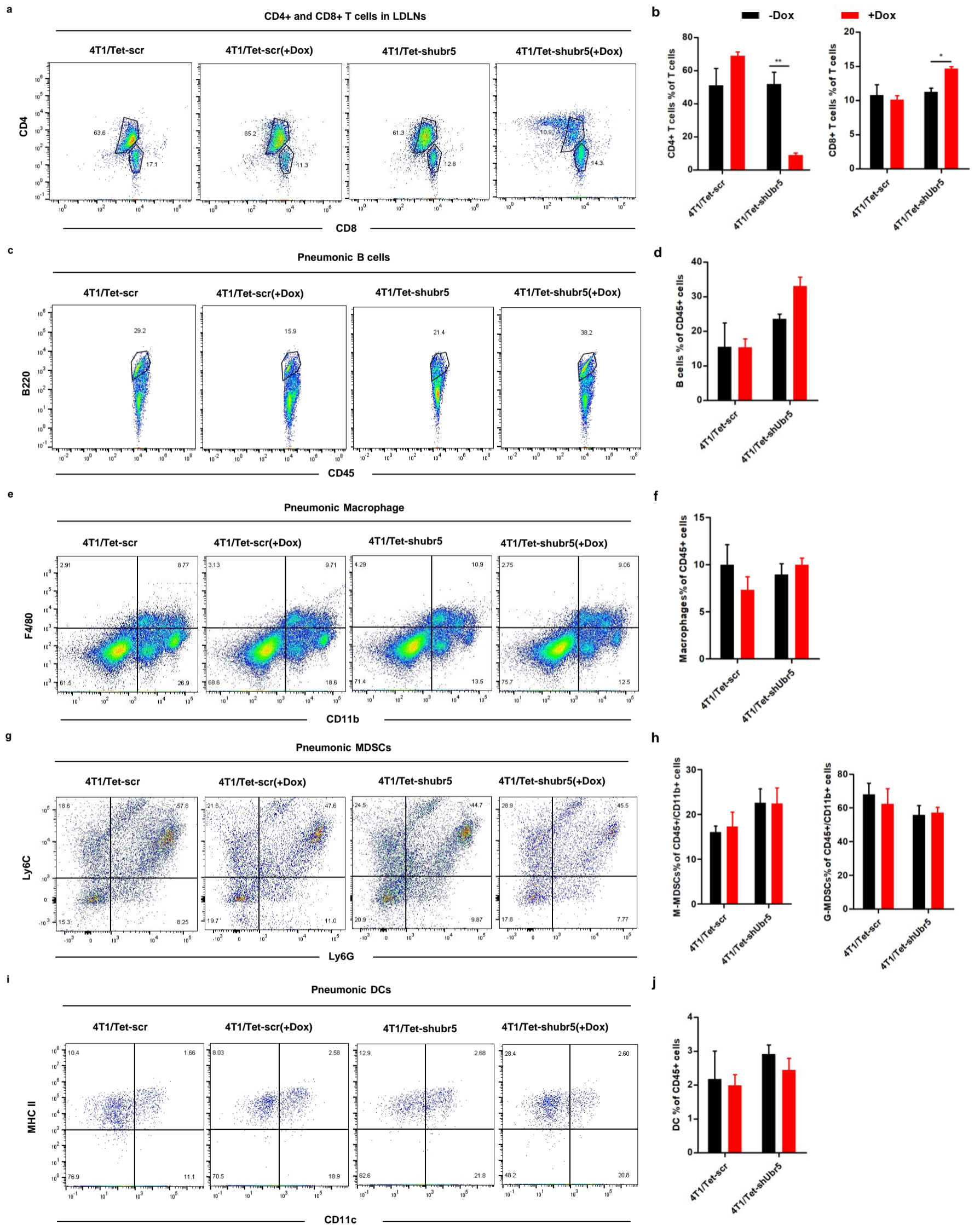


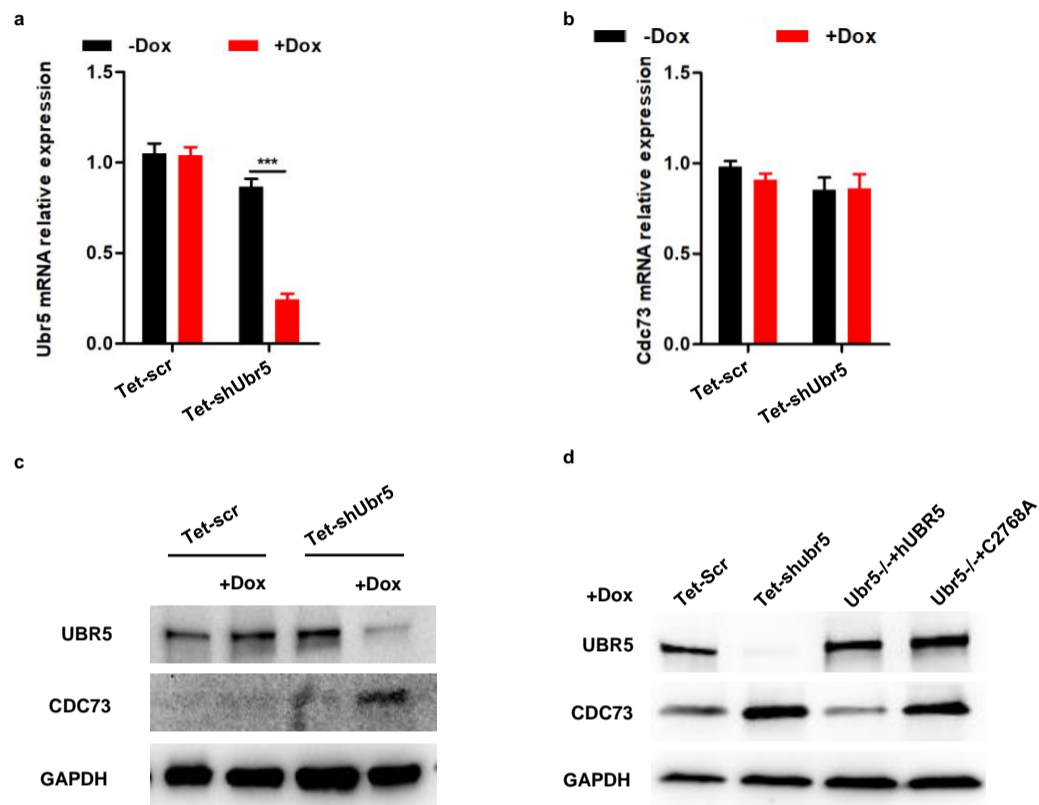
**Figure S1: The effect of different concentration of doxycycline in downregulating the expression of the protein of Ubr5 in vivo.** **a.** Schematic for knocking down Ubr5 expression with doxycycline. The BALB/c mice that injected with  $5 \times 10^5$  4T1/Tet-shUbr5 cells into mammary pad were treated with 200ul different concentration of doxycycline(5mg/ml, 10mg/ml, 20mg/ml) daily by gavage from day 3 and sacrificed on D 23 for analyze. **b.** Tumor growth curve of four groups. Tumor size was measured every 2 days. **c.** Tumors from orthotopic model were resected on day 23. **d.** The Ubr5 mRNA expression in 4T1 tumors bearing mice treated with different concentration of doxycycline was detected by real-time quantitative PCR and expressed as relative expression to that of GAPDH. **e.** The weight curve after doxycycline addition. Data represent mean  $\pm$  SEM; \*P <0.05; \*\*P <0.01; \*\*\*P < 0.001.



**Figure S2: The tumor volume and lung metastases before primary tumor removal surgery.** **a.** Schematic for removing primary tumor and sacrificing mice for spontaneous metastases analyze.  $5 \times 10^5$  4T1/Tet-scrambled, 4T1/Tet-shUbr5, 4T1/Ubr5<sup>-/-</sup>+EDD, 4T1/Ubr5<sup>-/-</sup>+EDD-C2768A, 4T1/Tet-shCdc73, 4T1/Tet-shUbr5-shCdc73 cells were s.c. injected into the mammary pad of BALB/c mice. The mice were sacrificed for 6-thioguanine clonogenicity assay on day 23. **b.** Primary tumor volume were measured on the day of primary tumor removal surgery. **c.** The micro-metastases in the lung of mice bearing 4T1/Tet-scrambled and 4T1/Tet-shUbr5 cells before Dox addition were visualized and quantitated by the 6-thioguanine clonogenicity assay. **d.** The micro-metastases in the lung of mice were quantitated by the 6-thioguanine clonogenicity assay. **e.** The primary tumor volume was measured on day 20 after tumor cells inoculation.



**Figure S3: Immunological alterations in mice with inducible knock-down Ubr5 expression by Tet-on system.** 4T1 tumor cells were s.c. injected into the mammary pad of BALB/c mice and on day 35, mice were sacrificed and organs were harvest for FACS analysis after tumor removal on day 20. **a, b.** Representative FACS images(**a**) and quantification(**b**) of CD4 T cells and CD8 T cells in lung draining lymph nodes(LDLN). Representative FACS images of pneumonic B cells(**c**), macrophage(**e**), MDSCs(**g**) and DCs(**i**). Quantification of pneumonic B cells(**d**), macrophage(**f**), MDSCs(**h**) and DCs(**j**). In all cases, data are representative of at least three independent experiments using three to four mice per group. Data represent mean  $\pm$  SEM; \*  $P < 0.05$ ; \*\* $P < 0.01$ .



**Figure S4: The UBR5 and CDC73 mRNA and protein expression in 4T1 cells.** **a, b.** Ubr5 mRNA(a) and cdc73 mRNA(b) expression of 4T1/Tet-scrambled( $\pm$ Dox) and 4T1/Tet-shUbr5 ( $\pm$ Dox) cells was detected by real-time quantitative PCR. **c.** Protein expression of UBR5 and CDC73 in 4T1/Tet-scrambled( $\pm$ Dox) and 4T1/Tet-shUbr5 ( $\pm$ Dox) cells analyzed by Western blot. **d.** Protein expression of UBR5 and CDC73 in 4T1/Tet-scrambled(+Dox), 4T1/Tet-shUbr5 (+Dox), 4T1/ubr5-/-+EDD (+Dox), 4T1/ubr5-/-+C2768A (+Dox). Data represent mean  $\pm$  SEM; \*P < 0.05; \*\*P < 0.01; \*\*\*P < 0.001.