SUPPLEMENTARY INFORMATION

Supplementary Figures and Legends

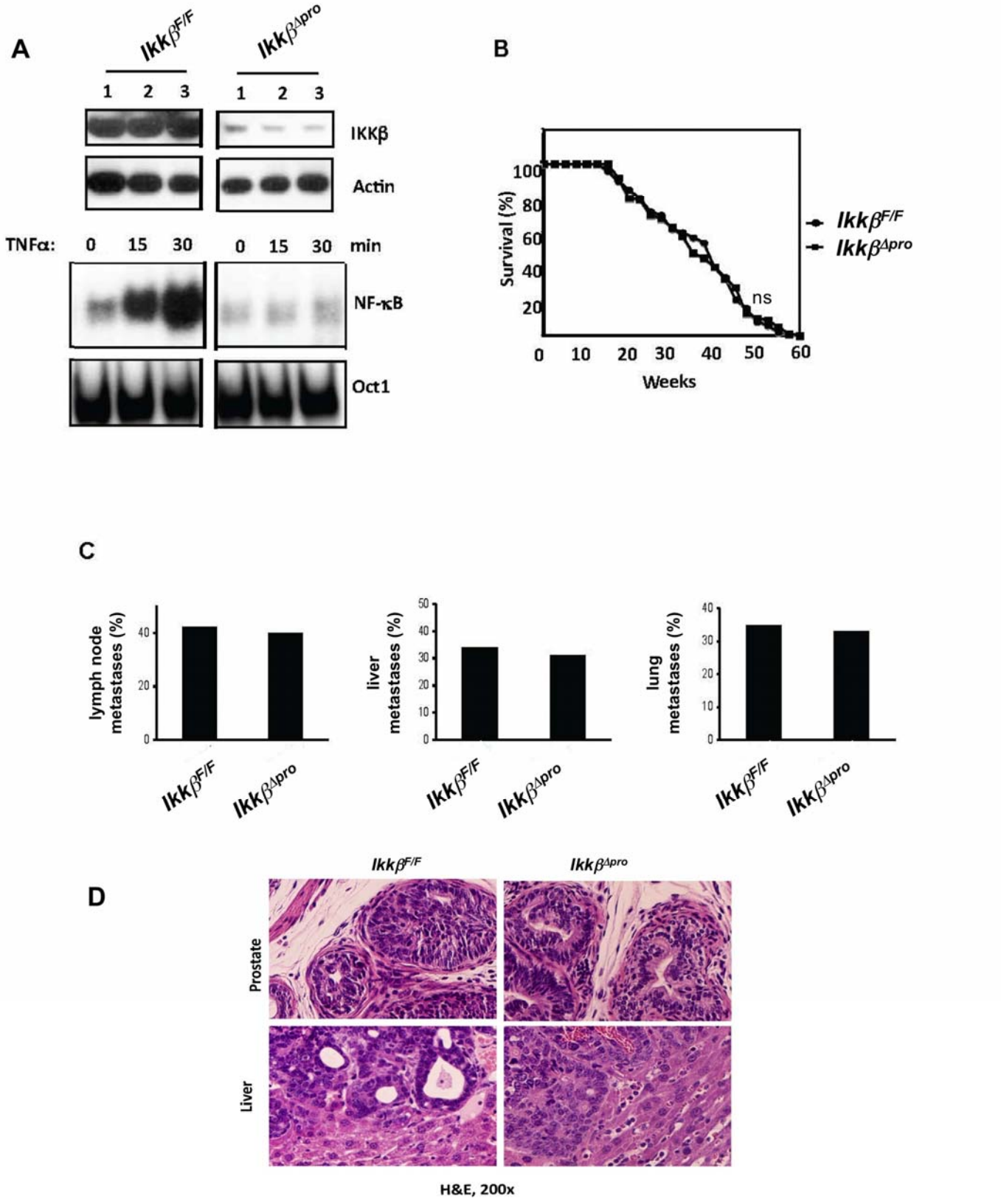

Figure S1. IKKβ in prostate epithelial cells has no effect on CaP progression and metastasis. A. The deletion efficiency of IKKβ in *Ikkβ*$^{F/F}$/*TRAMP* and *Ikkβ*$^{F/F}$*/TRAMP/PB-Cre4* (*Ikkβ*$^{\Delta pro}$) mice was analyzed. Primary prostate epithelial cells were isolated, cultured and stimulated with TNF-α (10 ng/ml). After 0, 15 and 30 min, cytoplasmic and nuclear extracts were prepared and analyzed for IKKβ expression (1,2,3 refer to different mice) or NF-κB and Oct-1 DNA binding activities. **B**. Survival of *Ikkβ*$^{F/F}$*/TRAMP* (n=21) and *Ikkβ*$^{\Delta pro}$*/TRAMP* (n=16) mice was compared by Kaplan-Meier analysis. P values were determined and are depicted as insignificant (ns), significant (*), very significant (**) or highly significant (***). **C.** Incidence of lymph node, liver and lung metastases in *Ikkβ*$^{F/F}$*/TRAMP* and *Ikkβ*$^{\Delta pro}$*/TRAMP* mice at time of death. **D.** Histological analysis of primary CaP and liver metastasis in *Ikkβ*$^{F/F}$*/TRAMP* and *Ikkβ*$^{\Delta pro}$*/TRAMP* mice.

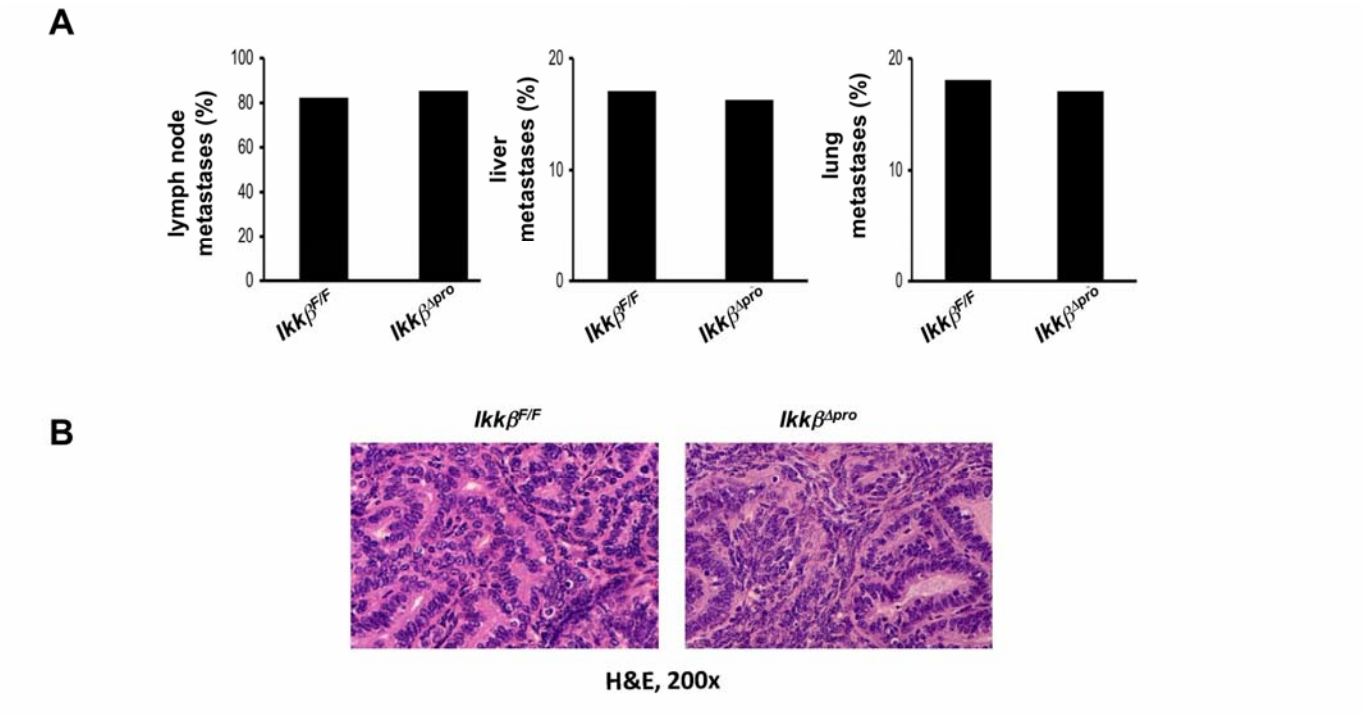

Figure S2. IKKβ in prostate epithelial cells has no effect on emergence of CR-CaP. A. Twenty-week old *Ikkβ*$^{\Delta pro}$*/TRAMP* (n=12) and *Ikkβ*$^{F/F}$*/TRAMP* (n=13) males were castrated. After 5 months, mice were sacrificed and incidence of lymph node, lung and liver metastases were determined. **B**. Histological analysis of primary prostate tumors from castrated *Ikkβ*$^{\Delta pro}$*/TRAMP* and *Ikkβ*$^{F/F}$*/TRAMP* mice.

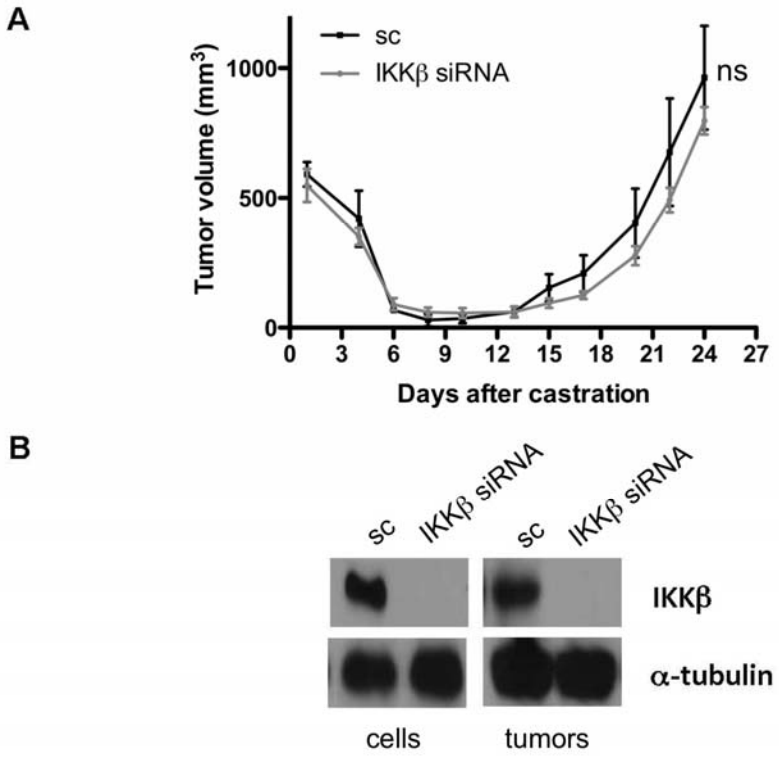

Figure S3. Silencing of IKKβ in CaP cells has no effect on emergence of CR-CaP. Male *FVB* mice were injected with myc-CaP cells, previously infected with lentiviruses expressing control (scrambled, sc) or IKKβ specific siRNAs. When tumors reached 900 mm^3, mice (n=10 per group) were castrated. **A.** Tumor size was measured every 2-3 days. Results are averages ± s.e.m. P value was determined and depicted as above. **B.** Myc-CaP cells were used for inoculation and the resulting tumors, collected at the end of the experiment, were analyzed for IKKβ expression.

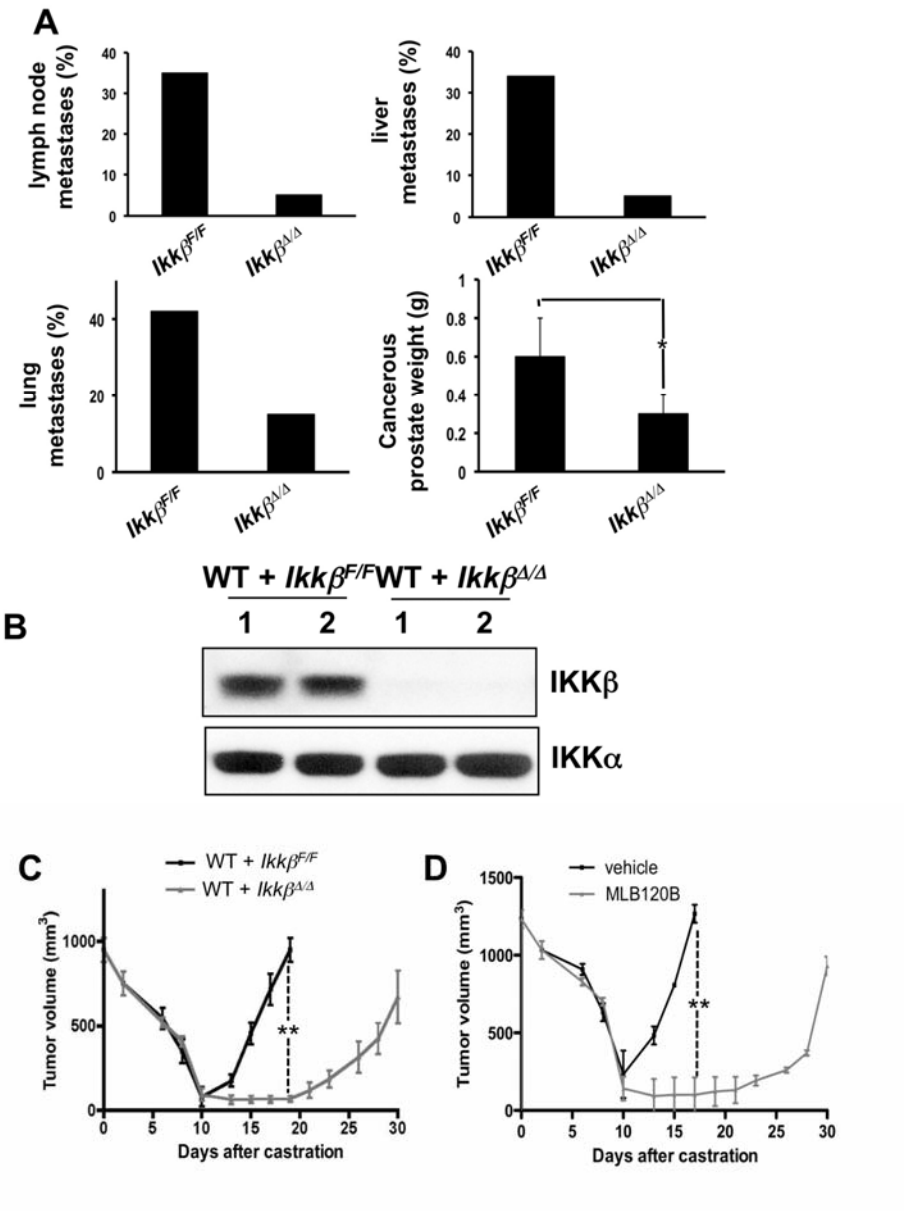

Figure S4. IKKβ deletion in BMDC retards CR-CaP appearance and metastasis. A. Twenty-week old *Ikkβ*$^{F/F}$*/TRAMP/Mx1-Cre* (*Ikkβ*$^{\Delta/\Delta}$*TRAMP*) and *Ikkβ*$^{F/F}$*/TRAMP* males (n=15-17) were injected three times with poly(IC) and castrated 3 days after last injection. Five months later, mice were sacrificed and prostate tumor weight and incidence of lymph node, lung and liver metastases were determined. **B.** Six weeks old *FVB* males were lethally irradiated and transplanted with BM of male *Ikkβ*$^{F/F}$ or *Ikkβ*$^{F/F}$*/Mx-1Cre* mice (n=10 each group). After 8 weeks, mice received 2 x 10^6 myc-CaP cells subcutaneously. When tumors reached 900 mm^3, mice were thrice injected with poly(IC) to delete IKKβ in BMDC and castrated 3 days later. IKKβ

deletion was examined by immunoblot analysis of peripheral leukocytes. **C.** Tumor volume in above mice was measured every 2-3 days. Results are averages $\pm$ s.e.m. (n=10). **D.** Six weeks old *FVB* mice (n=6 each group) were inoculated with myc-CaP cells and when tumors reached 1000 mm^3, were castrated and injected twice daily with vehicle or IKKβ inhibitor, ML120B. Tumor volume was measured as above. Results are averages $\pm$ s.e.m. P values were determined and depicted as above.

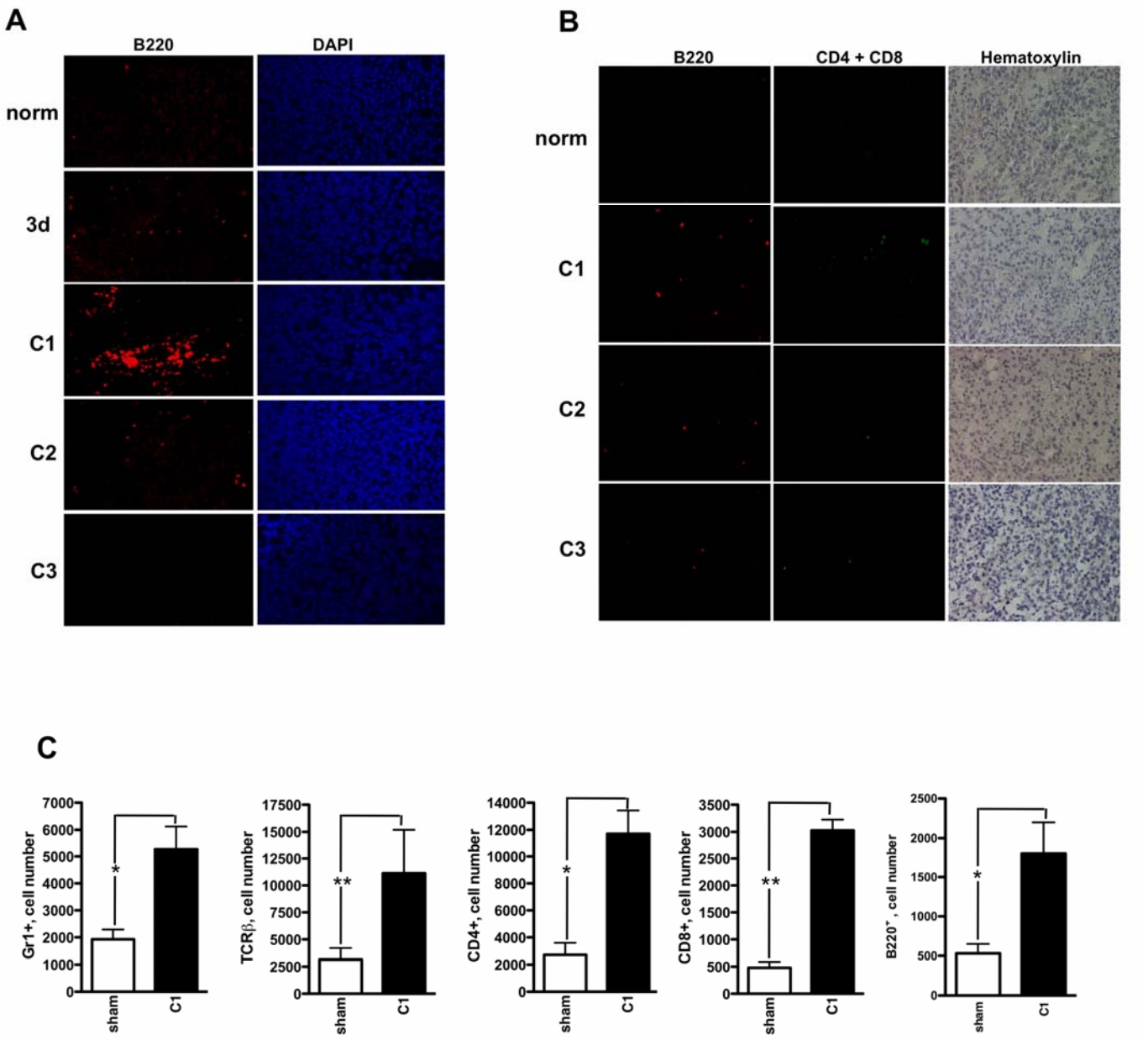

Figure S5. Distribution of B cells in tumors. Myc-CaP tumors were established in 6 weeks old *FVB* mice. When tumors reached 1000 mm^3, mice were left untreated (normal) or castrated. **A,B.** Tumors were collected either 3 days or 1, 2 or 3 weeks later. Frozen sections were stained with anti-B220 antibody or a combination of anti-CD4 and anti-CD8 antibodies, counterstained with DAPI or hematoxylin and analyzed by immunofluorescent microscopy. **C.** Myc-CaP tumors were established as above. When tumors reached 1000 mm^3, mice were sham operated or

castrated. Tumor samples were collected, digested with collagenase, stained with the indicated cell marker antibodies and analyzed by flow cytometry.

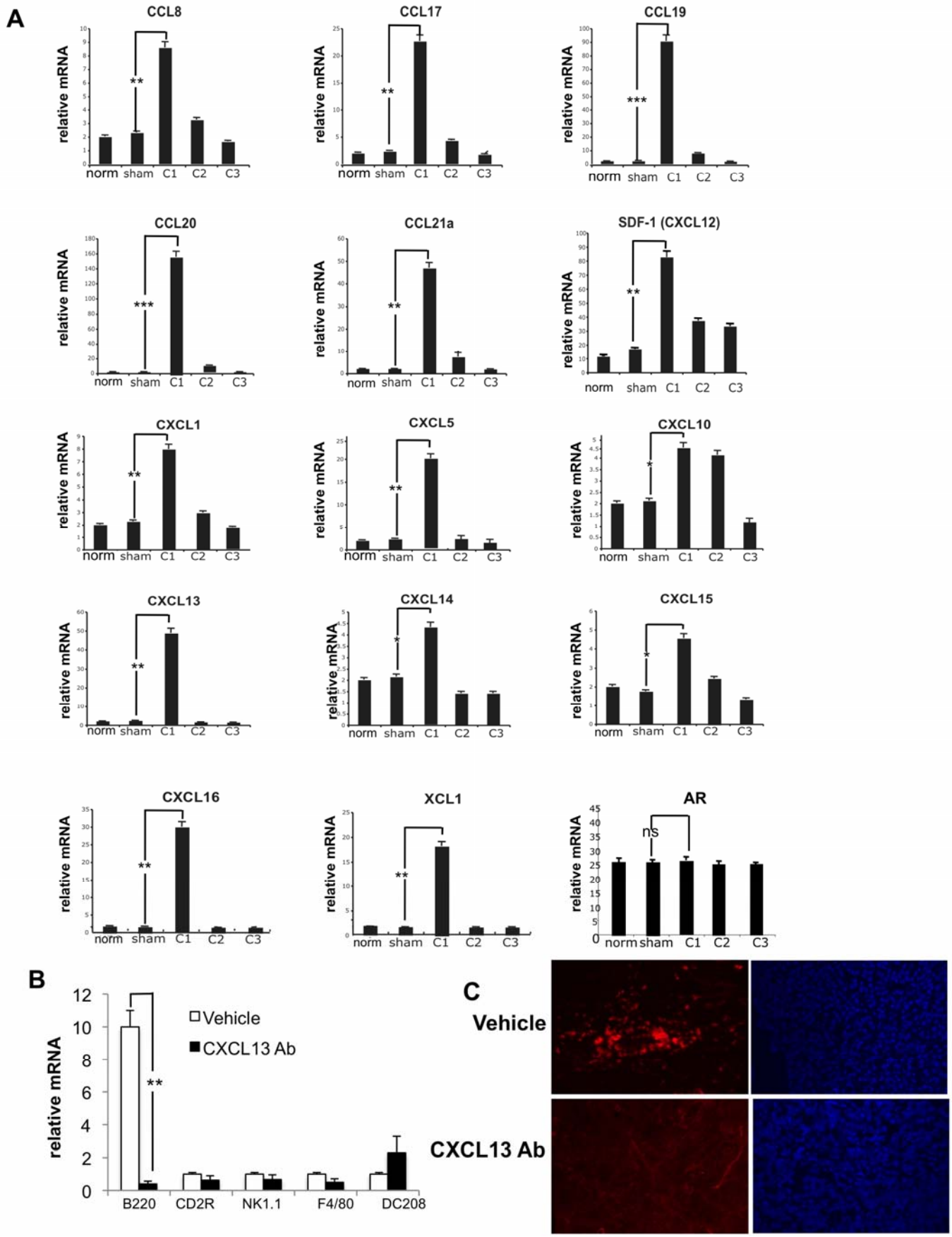
A
CCL8
CCL17
CCL19
CCL20
CCL21a
SDF-1 (CXCL12)
CXCL1
CXCL5
CXCL10
CXCL13
CXCL14
CXCL15
CXCL16
XCL1
AR
relative mRNA
norm sham C1 C2 C3
ns
B
Vehicle
CXCL13 Ab
B220 CD2R NK1.1 F4/80 DC208
C
Vehicle
CXCL13 Ab

Figure S6. Castration-induced regression of CaP results in induction of inflammatory chemokines in tumor remnants. A. Myc-CaP tumors were established in 6 weeks old *FVB* mice (n=10). When tumors reached 1000 mm^3, mice were left untreated (normal), sham operated or castrated and tumors were collected 1, 2 or 3 weeks later. Total RNA was isolated and expression of the indicated chemokine and AR mRNAs was quantitated by Q-PCR and normalized to the amount of cyclophilin A mRNA. Results are averages $\pm$ s.d. (n=3). P values for the difference in mRNA amounts between sham operated and castrated mice at week 1 were determined and depicted as above. **B.** Myc-CaP tumors were established as described above. Three days before castration mice were injected i.p. with 200 μg of CXCL13 neutralizing antibody or vehicle (PBS). Tumor samples were collected one week after castration. Total RNA was isolated and expression of the indicated cellular marker mRNAs was quantitated by Q-PCR and normalized to the amount of cyclophilin A mRNA. Results are averages $\pm$ s.d.. P values were determined and depicted as above. **C.** Frozen sections of SC tumors were stained with anti-B220, counterstained with DAPI and analyzed by immunofluorescent microscopy.

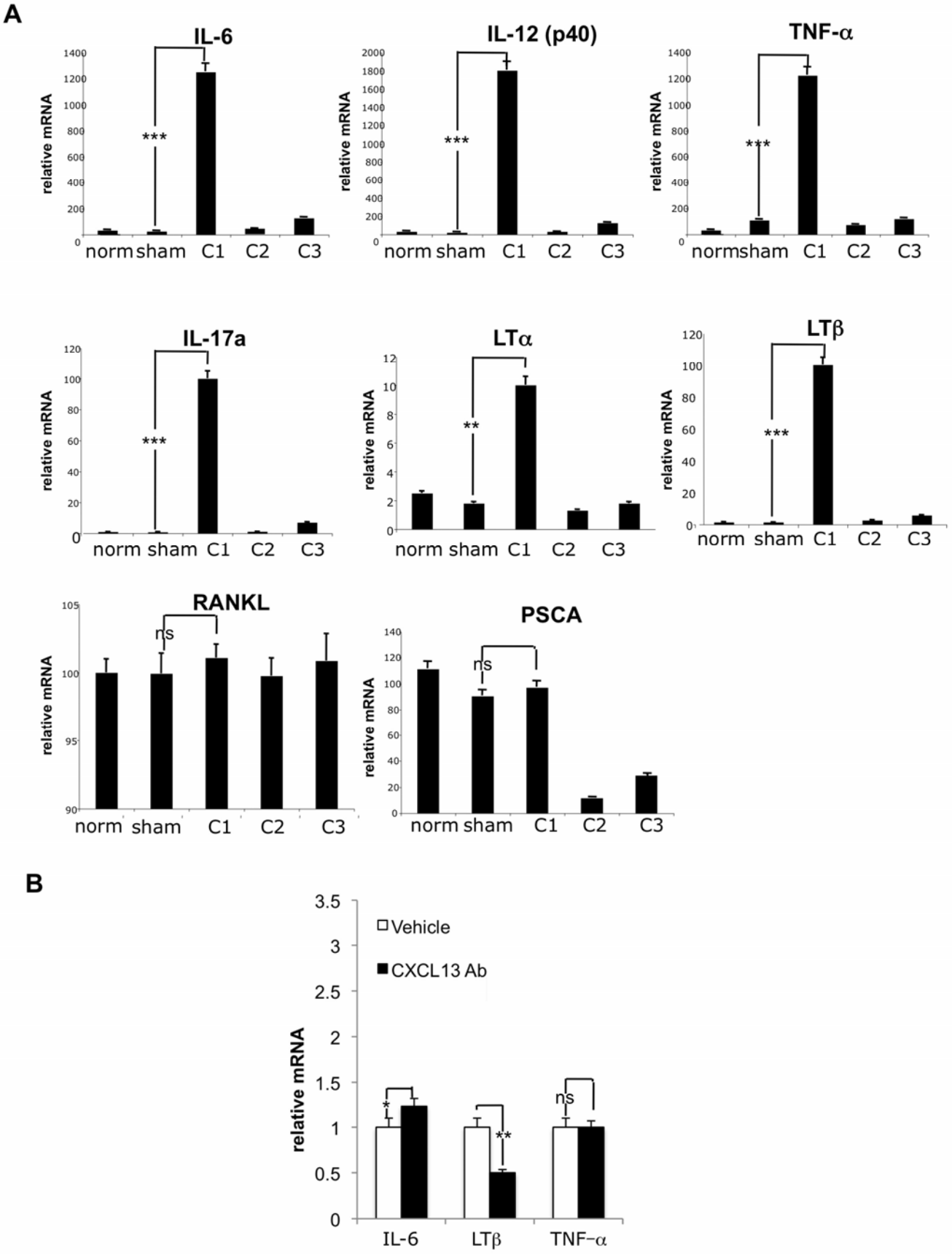
A
IL-6
IL-12 (p40)
TNF-α
IL-17a
LTα
LTβ
RANKL
PSCA
relative mRNA
norm
sham
C1
C2
C3
***
**
ns
B
Vehicle
CXCL13 Ab
IL-6
LTβ
TNF−α
*
**
ns

Figure S7. Castration-induced regression of CaP results in induction of inflammatory cytokines in tumor remnants. A. Total RNA was isolated from tumor samples starting 1 week after castration of the mice described above (Fig. S6) and analyzed for expression of the indicated cytokines or prostate stem cell antigen (PSCA) mRNAs as above. **B.** Total RNA was isolated from the samples described in Fig. S5B and analyzed for expression of the indicated cytokine mRNAs (n=3). P values were determined and depicted as above.

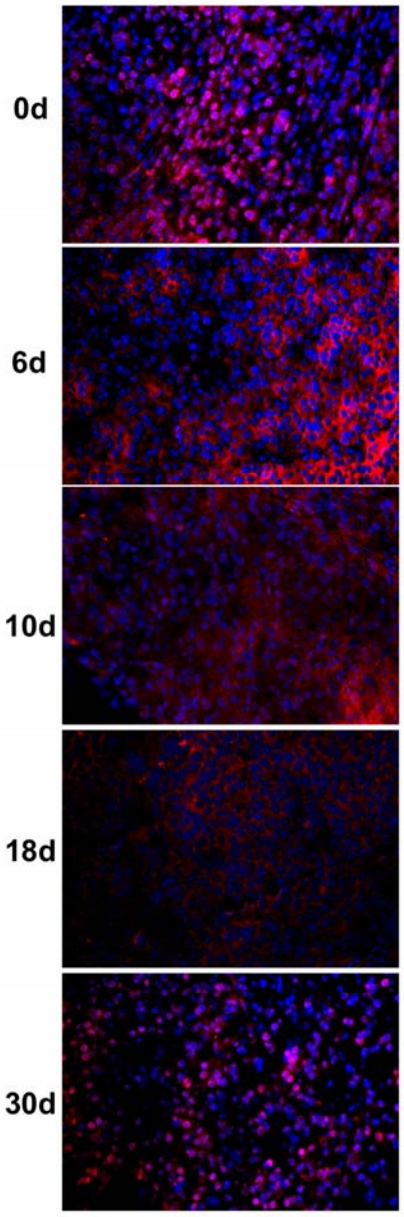

Figure S8. AR localization during the emergence of CR-CaP. Myc-Cap tumors were established in *FVB* male mice. Tumor samples were collected at the indicated time points after castration and analyzed for AR localization by immunofluorescent microscopy. Nuclear AR is seen in tumors from non-castrated mice (0 d) and 30 days after castration.

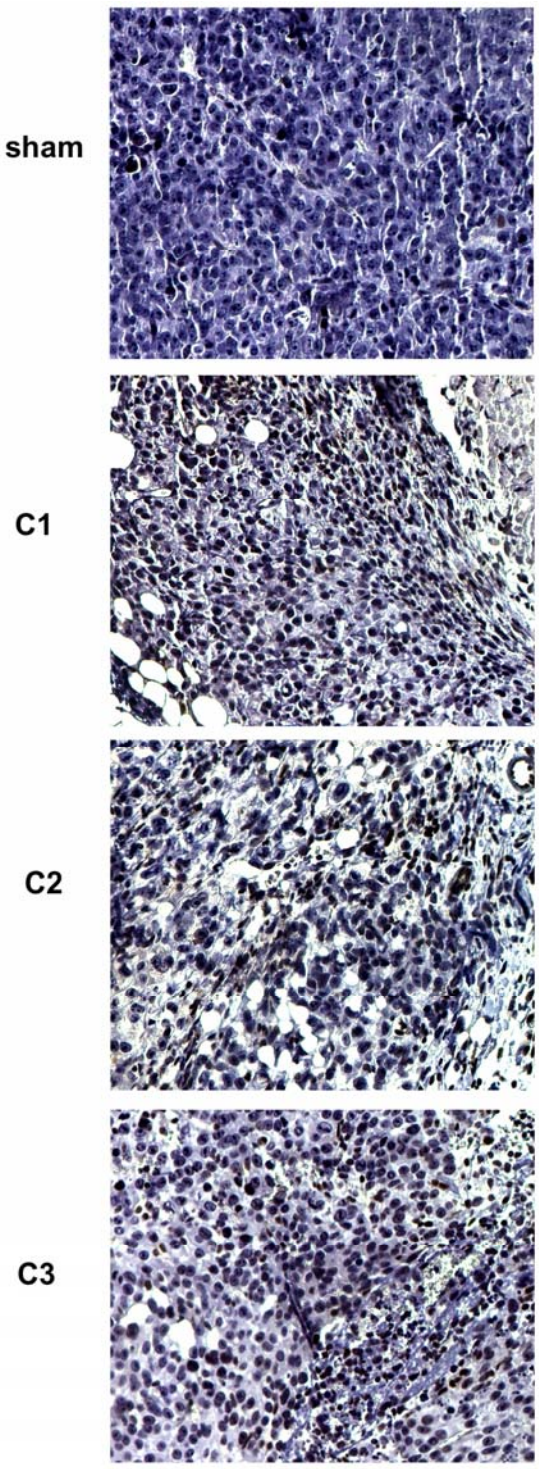

Figure S9. STAT3 is phosphorylated after castration. Myc-CaP tumors were established as described above. Tumor samples were collected at the indicated time points after castration or

sham operation. Paraffin-embedded sections were analyzed for STAT3 phosphorylation by staining with phospho-STAT3 antibody.

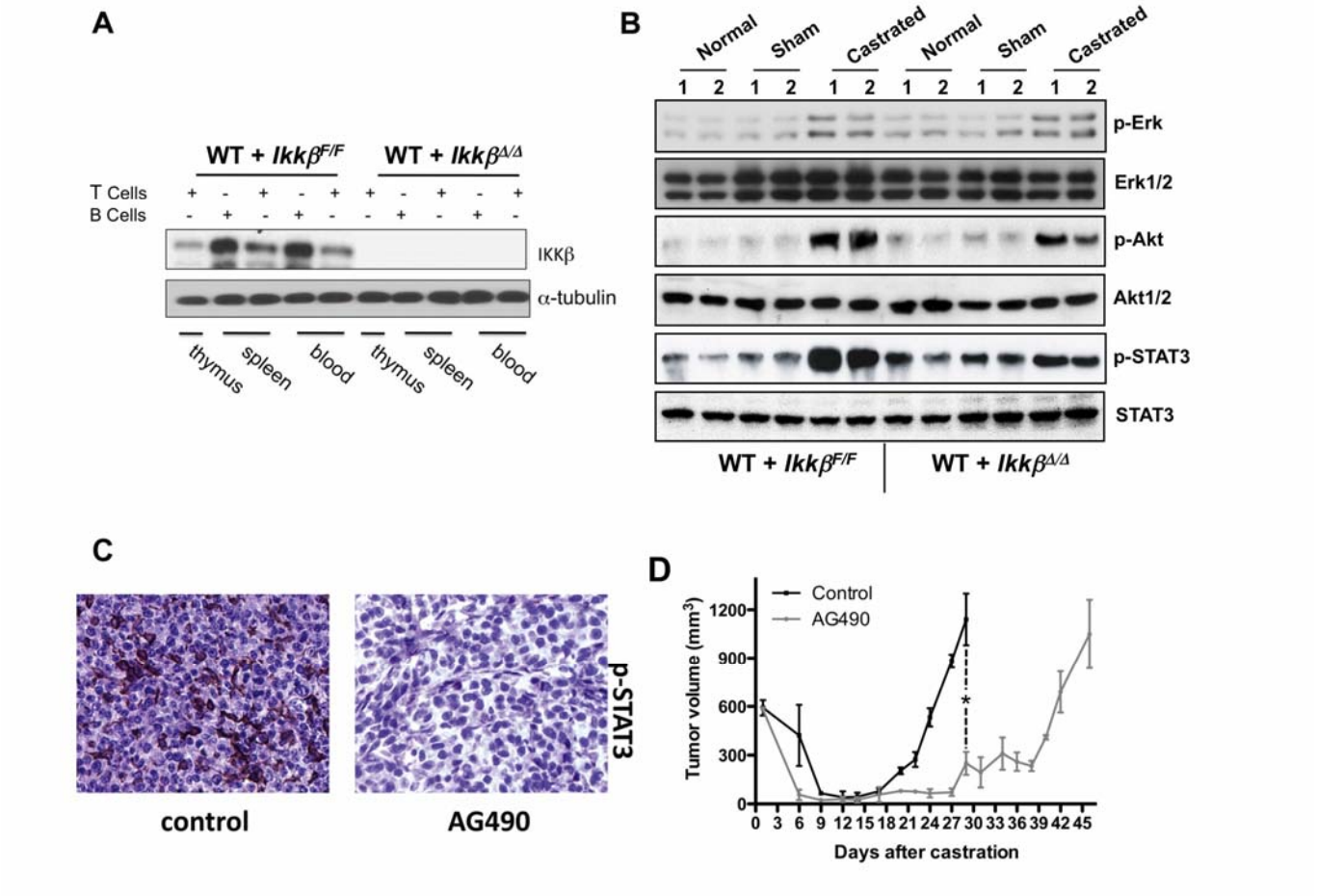

Figure S10. STAT3 activation and its role in CR-CaP emergence. A,B WT + *Ikkβ*$^{F/F}$ and WT + *Ikkβ*$^{Δ/Δ}$ radiation chimeras (n=10 each group) bearing myc-CaP allografts were established as above and injected with poly(IC) to delete IKKβ in BMDC before castration or sham operation. After one month, mice were sacrificed for analysis. **A.** Lymphocytes were isolated from indicated tissues and analyzed for IKKβ expression. **B.** Tumor samples were immunoblotted to determine expression and phosphorylation of indicated signaling proteins. **C,D** *FVB* mice bearing myc-CaP tumors were castrated. Starting one day before castration, the mice (n=10 per group) were injected twice daily with vehicle or AG490, an inhibitor of STAT3 phosphorylation. **C.** One week after castration, tumors were collected, paraffin-embedded, sectioned and stained with phospho-STAT3 antibody. **D.** Tumor volume was measured every 2-3 days as above. Results are averages ± s.e.m.. P values were determined and are indicated as above.

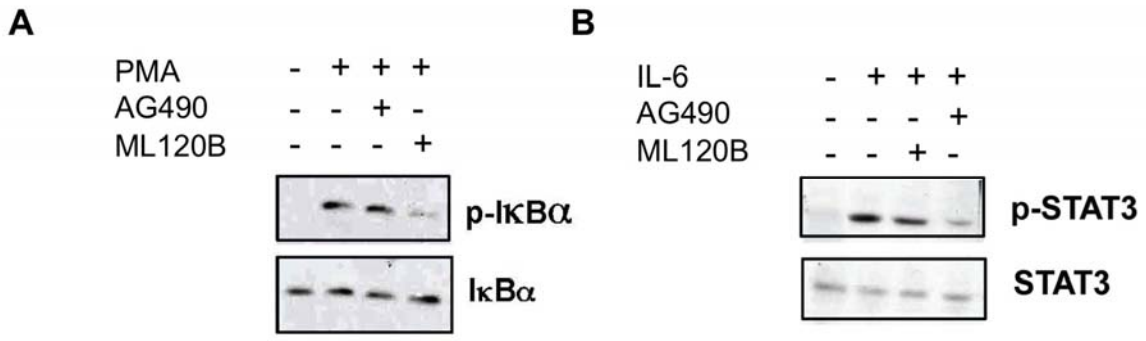

Figure S11. Selectivity of IKKβ and STAT3 phosphorylation inhibitors. A. Myc-CaP cells were cultured to 60% confluency and pre-treated for 1 hr with AG490 (100 μM) or ML120B (20 μM), followed by stimulation with PMA (10 ng/ml) for 10 min. Cells were collected and IκBα phosphorylation was analyzed. **B.** Myc-CaP cells were pre-treated with AG490 or ML120B and after 1 hr, were stimulated with IL-6 (20 ng/ml) for 30 min. Cells were collected and STAT3 phosphorylation was analyzed by immunoblotting.

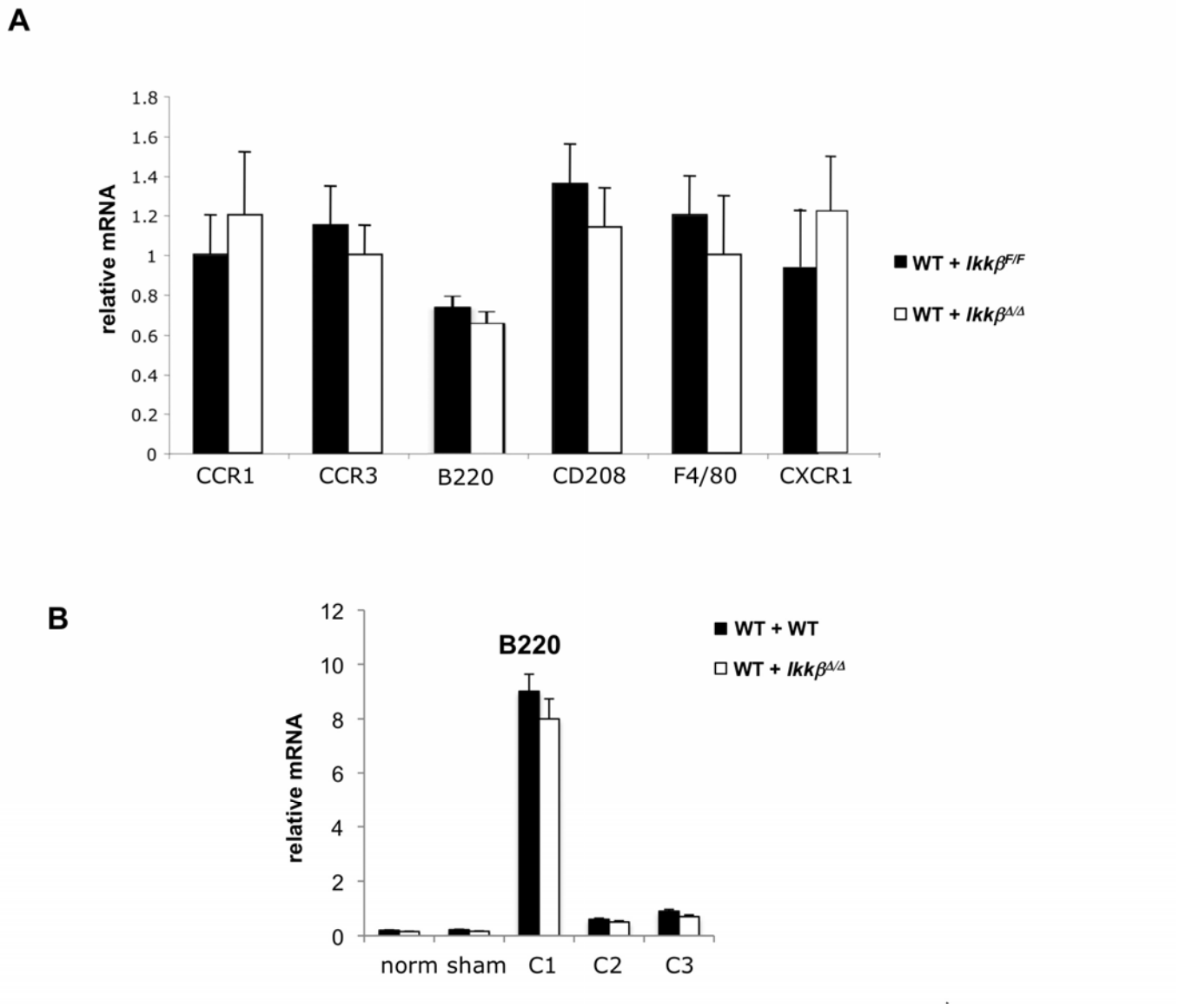

Figure S12. Deletion of IKKβ in bone marrow derivatives has no effect on infiltration of leukocytes into androgen-deprived tumors. Myc-CaP tumors were established in lethally irradiated *FVB* males that were reconstituted with $Ikk\beta^{F/F}$or $Ikk\beta^{\Delta/\Delta}$ BM. $Ikk\beta^{F/F}$ and $Ikk\beta^{\Delta/\Delta}$ chimeras were injected with poly(IC) as described above prior to castration. **A.** One week after castration, tumor samples were collected and total RNA was isolated and expression of indicated cell marker and chemokine receptor mRNAs was quantitated by Q-PCR and normalized to that of cyclophilin A mRNA. Results are averages ± s.d. (n=6). **B.** Tumor samples were collected as above from non-operated (norm), sham operated and castrated mice and expression of B220 mRNA was quantitated as above. Results are averages ± s.d. (n=5).

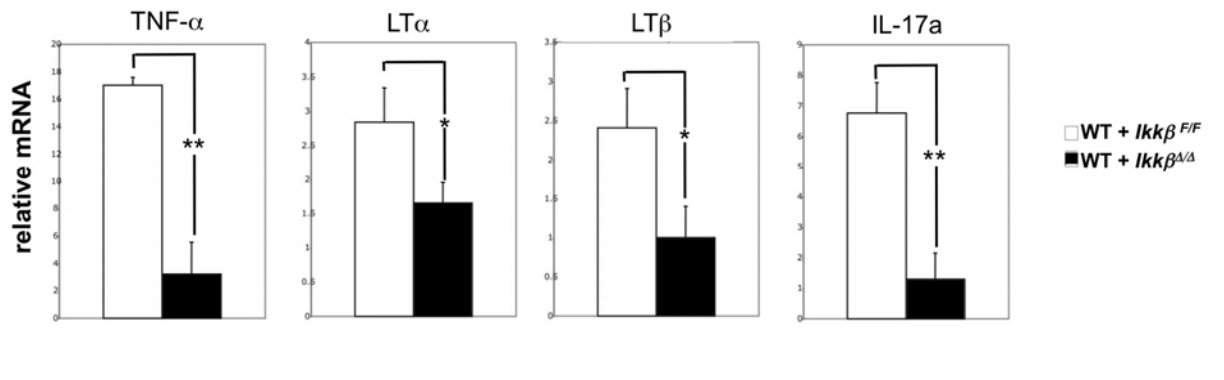

Figure S13. Castration-induced regression of AD-CaP induces expression of cytokines in an IKKβ-dependent manner. Myc-CaP tumors were established in WT + $Ikk\beta^{F/F}$ and WT + $Ikk\beta^{\Delta/\Delta}$ radiation chimeras. When tumors reached 1000 mm^3, mice were castrated and one week later, tumor samples were collected. Expression of the indicated cytokine mRNAs was analyzed by Q-PCR and normalized to cyclophilin A mRNA. Results are averages $\pm$ s.d. (n=5). P values were determined and depicted as above.

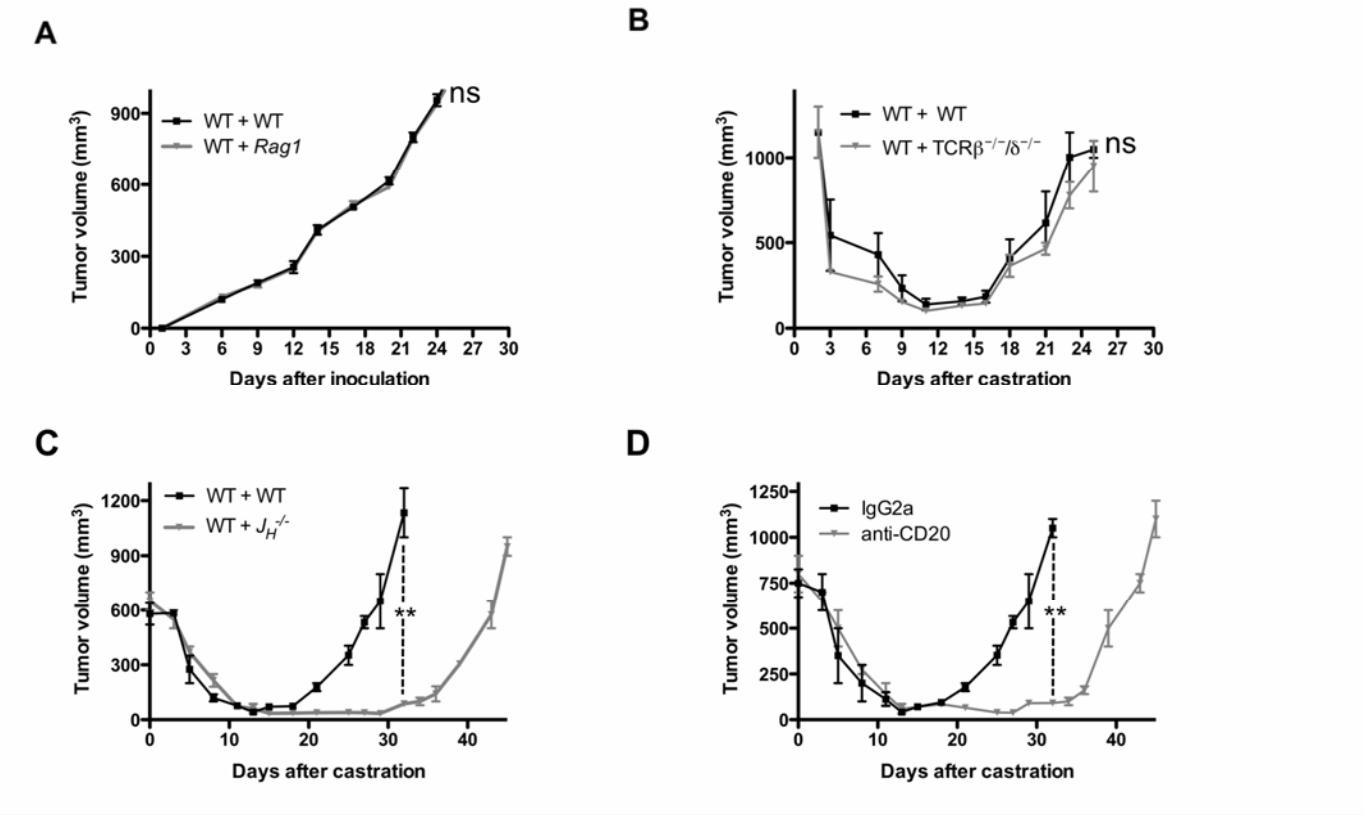

Figure S14. Lymphocytes are not required for primary CaP growth but B cells rather than T cells accelerate appearance of CR-CaP. A. Lethally irradiated *FVB* male mice (n=10 per group) were reconstituted with WT or *Rag1*$^{-/-}$ BM. After 8 weeks, myc-CaP cells were implanted and their growth monitored. **B.** Lethally irradiated *FVB* male mice (n=10 per group) were reconstituted with BM of WT (WT + WT) or T cell deficient *Tcrβ*$^{-/-}$/*δ*$^{-/-}$ mice (WT + *Tcrβ*$^{-/-}$*δ*$^{-/-}$). After 8 weeks, myc-CaP tumors were established and the mice were castrated when tumors reached 1000 mm^3. Tumor volume was measured as above. **C.** Lethally irradiated *FVB* male mice (n=10 per group) were reconstituted with BM of WT (WT + WT) or B cell deficient $J_H^{-/-}$ (WT + $J_H^{-/-}$) mice. After 8 weeks, myc-CaP tumors were established and the mice were castrated when tumors reached 1000 mm^3. Tumor volume was monitored as above. P values were determined and depicted as above. **D.** *FVB* mice (n=5 each group) were inoculated with myc-CaP cells, castrated as above and were given by i.p. injection IgG2a or anti-CD20 (200 μg)

every 5 days, starting 4 days before castration. Tumor volume was measured as above. Results are averages ± s.e.m..

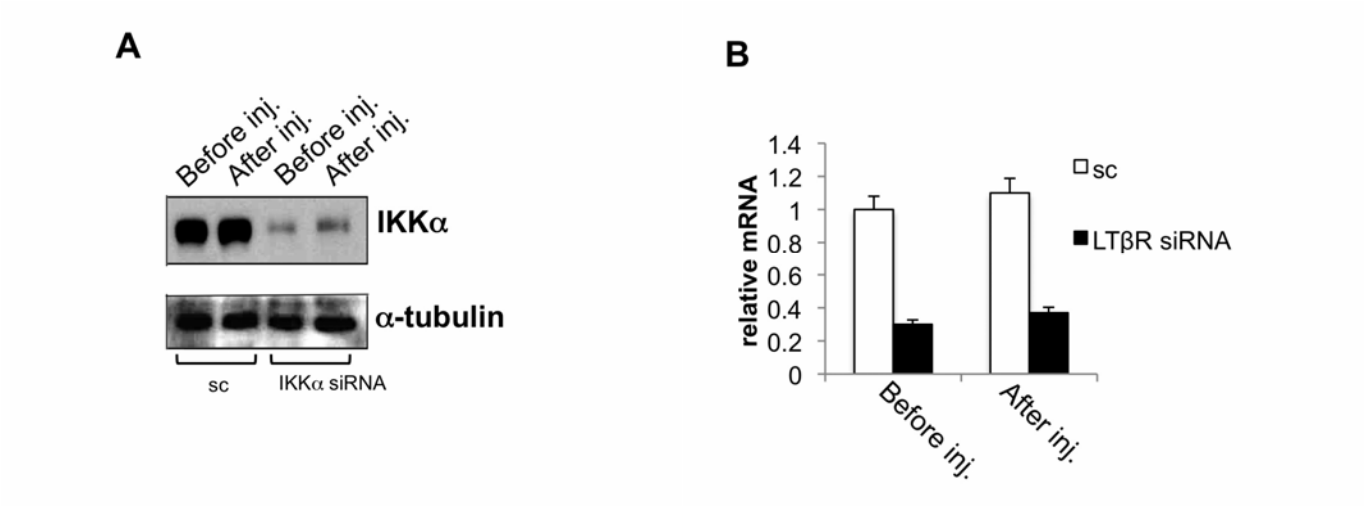

Figure S15. siRNA-mediated IKKα and LTβR silencing. A. Myc-CaP cells infected with lentiviruses encoding scrambled (sc) or IKKα siRNA were analyzed before implantation or after generation of tumor allografts for IKKα expression. **B.** LTβR mRNA was analyzed by Q-PCR and normalized to cyclophilin A in myc-CaP cells infected with lentiviruses encoding scrambled (sc) or LTβR siRNA before implantation or after generation of tumor allografts.

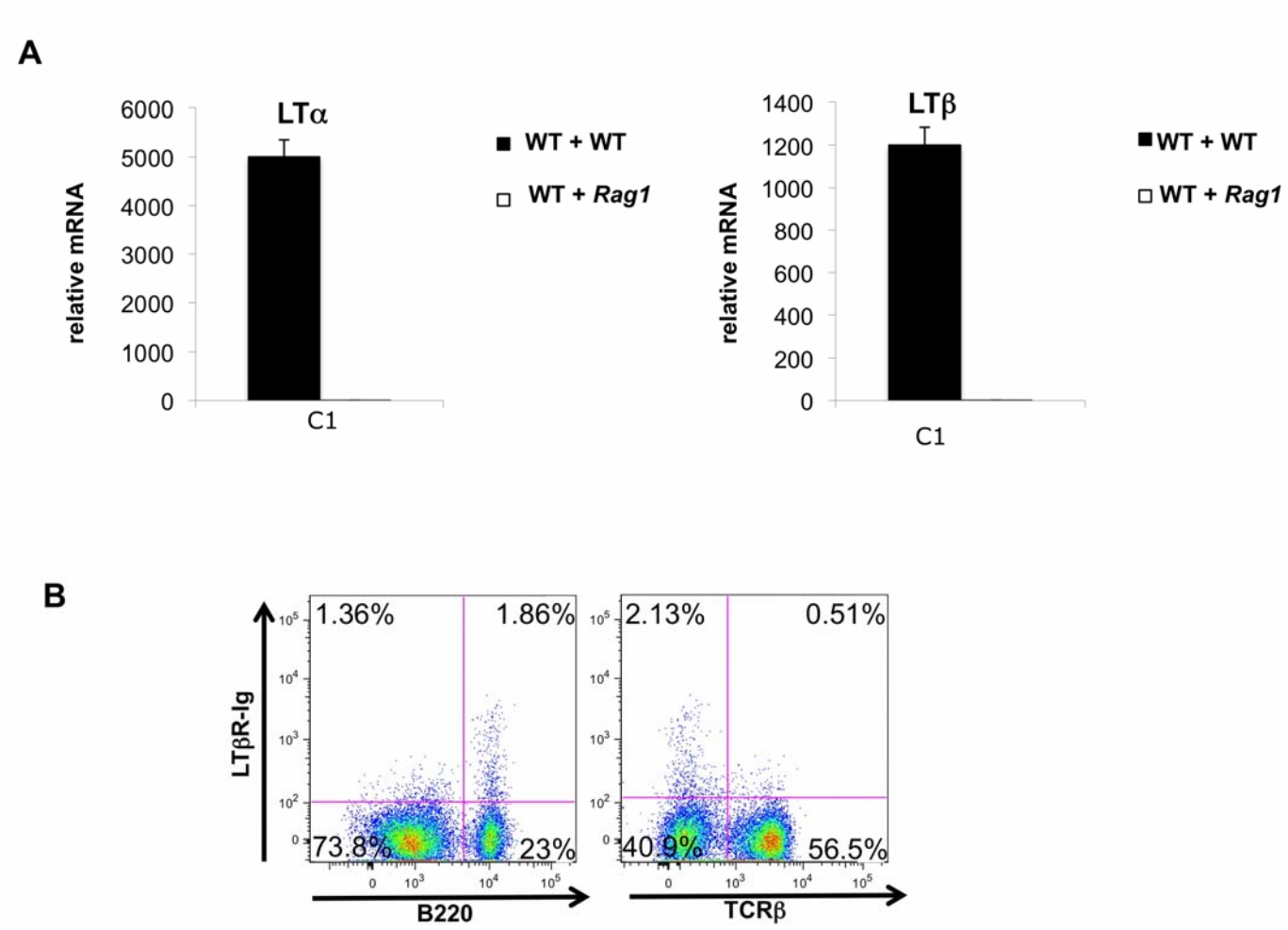

Figure S16. LT production in tumors is significantly reduced in the absence of lymphocytes and is localized mainly to B cells. A. Lethally irradiated *FVB* males were reconstituted with BM from *Rag1*$^{-/-}$ as described above. Tumors were established, collected 1 week after castration and total RNA was isolated. Expression of LTα and LTβ mRNAs was quantitated by Q-PCR and normalized to that of cyclophilin A mRNA. Results are averages ± s.d. (n=5). **B.** Myc-CaP tumors were established in FVB mice. One week after castration the tumors were removed, treated with collagenase and single cell suspension stained with LTβR-Ig fusion protein and either B220 or TCRβ antibodies and analyzed by flow cytometry.

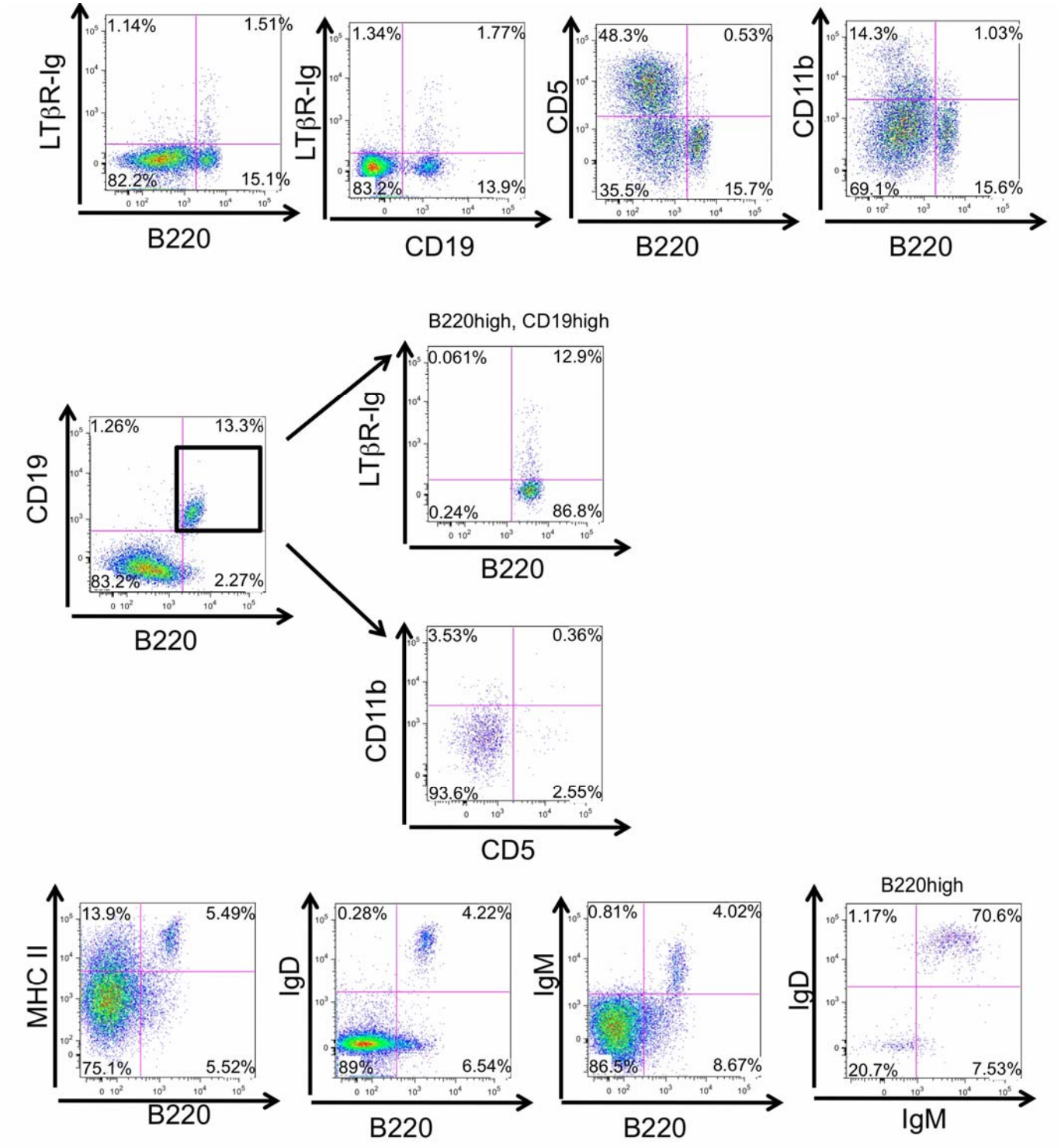

Figure S17. Characterization of tumor infiltrating B cells. Subcutaneous myc-CaP tumors were isolated one week after castration and digested with collagenase to prepare a single cell suspension that was filtered through a cell strainer. The cells were then stained with fluorescently-labeled antibodies to CD45, B220, CD19, IgD, IgM, CD11b, MHC class II and CD5

as well as LTβR-Ig fusion protein followed by anti-human Ig-PE antibody (Jackson Immunoresearch) and Aqua LIVE/DEAD dye (Molecular Probes). The stained cells were analyzed by flow cytometry on a BD LSRII instrument. Live hematopoietic cells were gated as $CD45^+$ $Aqua^-$. Shown are representative dot plots from one typical tumor.

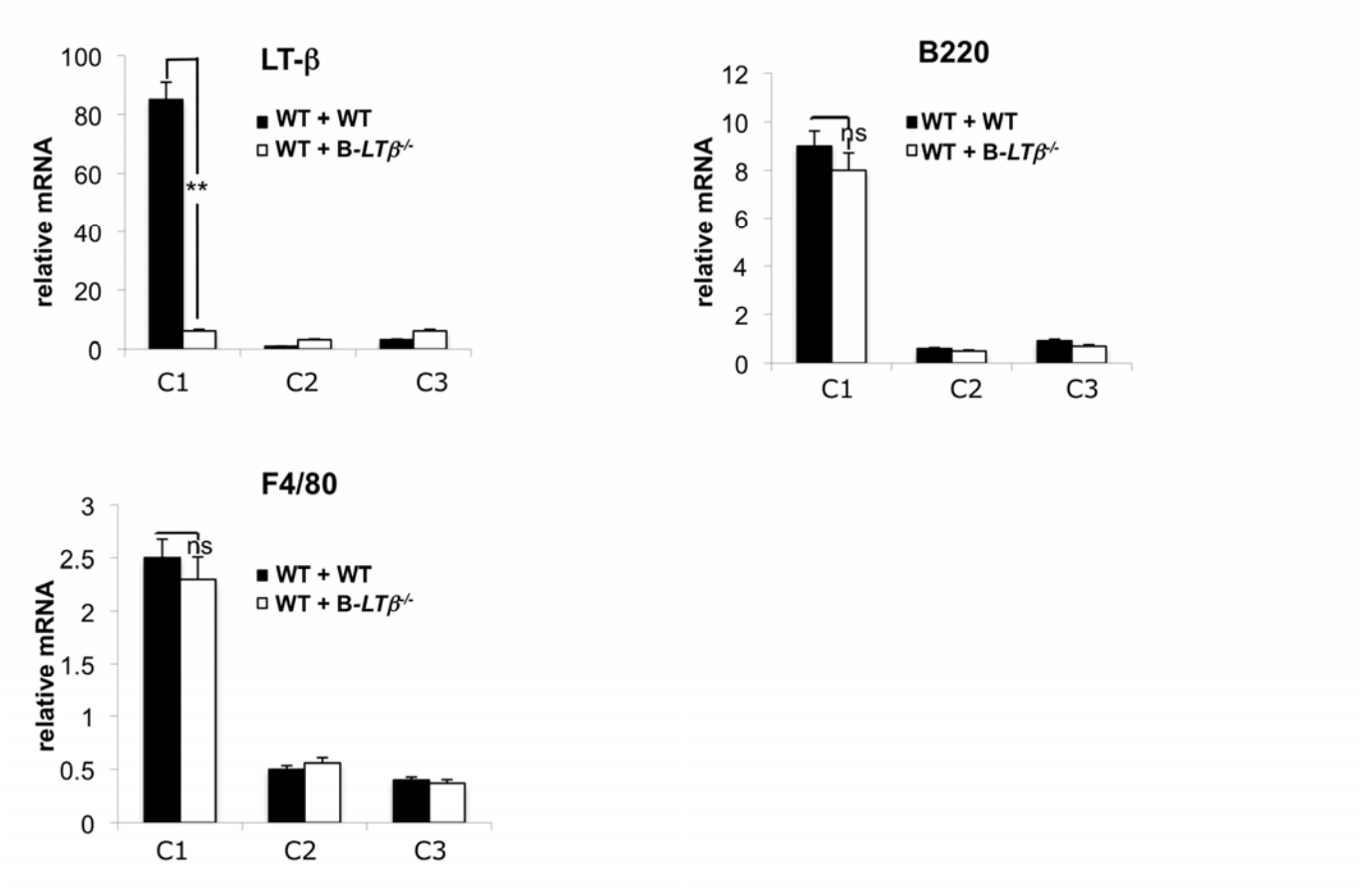

Figure S18. B cell-specific LTβ knockout abolishes LTβ expression in tumors but has no effect on B cell and macrophage infiltration. Lethally irradiated *FVB* males were reconstituted with BM from B-*Ltβ*$^{-/-}$ mice as described above. Tumors were established and collected at the indicated times after castration. Total RNA was isolated and expression of the indicated mRNAs was quantitated by Q-PCR and normalized to that of cyclophilin A mRNA. Results are averages ± s.d. (n=5). P values were determined and depicted as above.

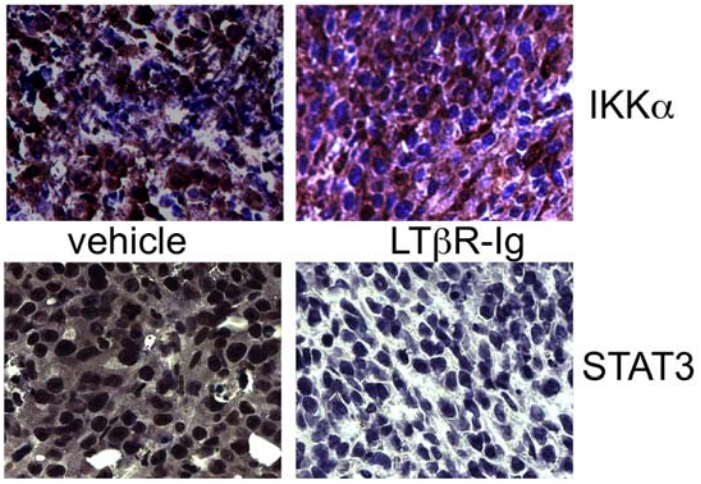

Figure S19. LTβ is required for IKKα nuclear localization and STAT3 phosphorylation. Mice carrying Myc-CaP tumors were castrated and treated with vehicle or LTβR-Ig as described above. Paraffin-embedded sections were analyzed for IKKα nuclear localization and STAT3 phosphorylation.

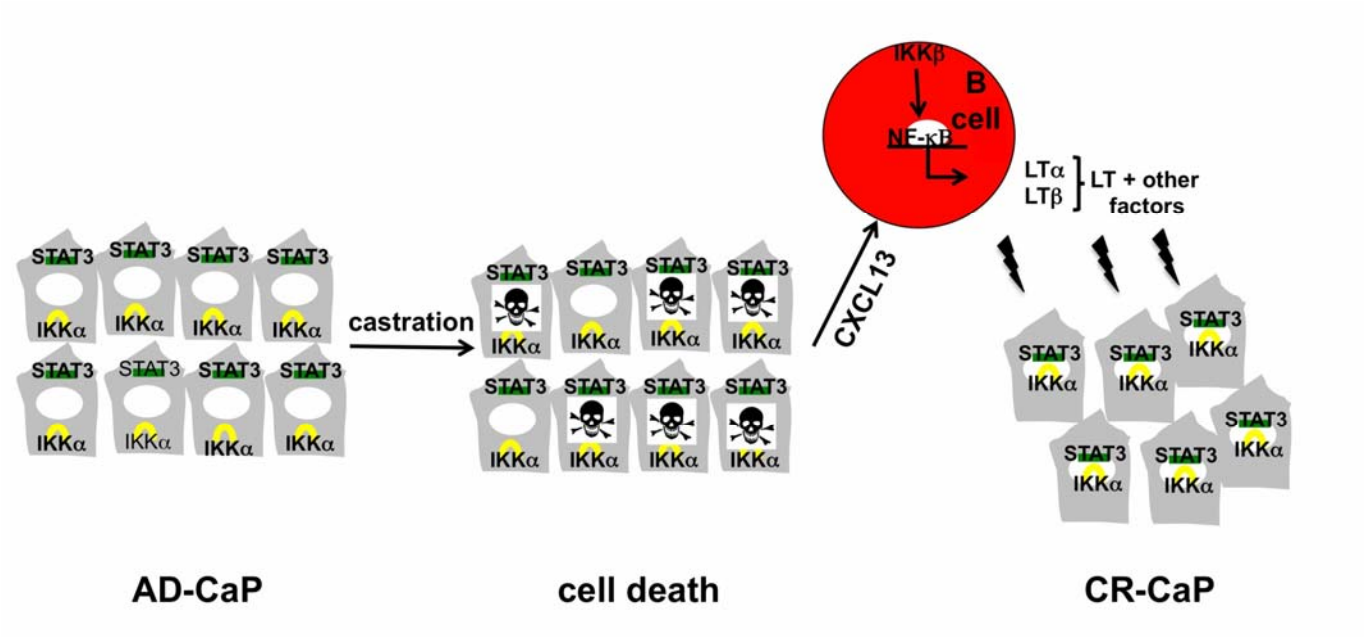

Figure S20. A model explaining how therapy-induced inflammation promotes emergence of CR-CaP. Androgen withdrawal causes death of primary AD-CaP cells, which release inflammatory mediators that lead to chemokine induction and recruitment of inflammatory cells, including B cells, into the tumor remnant. IKKβ activation in B cells results in NF-κB-dependent production of LT and other factors that activate IKKα and STAT3 in surviving CaP cells. This results in survival and re-growth of CR-CaP.

Supplementary Methods

Mice and cell culture

Ikkβ$^{F/F}$ (*BL6*) mice were crossed to *TRAMP* (*BL6*x*129*) mice[1] and *PB-Cre4* (*BL6*)[2] or *Mx1-Cre* (*BL6*) mice[3] to generate *TRAMP*$^{+/-}$/*Ikkβ*$^{+/F}$/*PB-Cre4*$^{+/-}$ and *TRAMP*$^{+/-}$/*Ikkβ*$^{+/F}$/*PB-Cre4*$^{+/+}$ or *TRAMP*$^{+/-}$/*Ikkβ*$^{+/F}$/*Mx1-Cre*$^{+/-}$ and *TRAMP*$^{+/-}$/*Ikkβ*$^{+/F}$/*Mx1-Cre*$^{+/+}$ progeny that were intercrossed with *TRAMP* mice for six generations. After that, *TRAMP*$^{+/-}$/*Ikkβ*$^{+/F}$/*PB-Cre4*$^{+/-}$ and *TRAMP*$^{+/-}$/*Ikkβ*$^{+/F}$/*PB-Cre4*$^{+/+}$ or *TRAMP*$^{+/-}$/*Ikkβ*$^{+/F}$/*Mx1-Cre*$^{+/-}$ and *TRAMP*$^{+/-}$/*Ikkβ*$^{+/F}$/*Mx1-Cre*$^{+/+}$ mice were intercrossed to generate *TRAMP*$^{+/-}$/*Ikkβ*$^{F/F}$/*PB-Cre4*$^{+/-}$, *TRAMP*$^{+/-}$/*Ikkβ*$^{F/F}$/*PB-Cre4*$^{+/+}$, *TRAMP*$^{+/-}$/*Ikkβ*$^{F/F}$/*Mx1-Cre*$^{+/-}$ and *TRAMP*$^{+/-}$/*Ikkβ*$^{F/F}$/*Mx1Cre*$^{+/+}$ mice. Only male littermates were used. *FVB*, *Tcrβ*$^{-/-}$*δ*$^{-/-}$ *(BL6)*, *Mx1-Cre* and *Rag1*$^{-/-}$ (*BL6*x*129*) mice were from the Jackson Laboratory. $J_H^{-/-}$ mice *(FVB)* were kindly provided by L. Coussens (Cancer Research Institute and Anatomic Pathology, UCSF, San Francisco, CA). Bone marrow from B-*Ltβ*$^{-/-}$ or T-*Ltβ*$^{-/-}$ mice[4] was kindly provided by C.F. Ware (La Jolla Institute for Allergy and Immunology, La Jolla, CA). *PB-Cre4* and *TRAMP* mice were from MMHCC (Mouse Models of Human Cancer Consortium). Mice were maintained under specific pathogen-free conditions, and experimental protocols were approved by the UCSD Animal Care Program, following NIH guidelines. Radiation chimeras were generated as described[5]. In general, irradiated *FVB* mice were reconstituted with bone marrow from different strains that have been backcrossed to the *FVB* background for at least 2 generations. However, in the case of B-*Ltβ*$^{-/-}$ and T-*Ltβ*$^{-/-}$ mice, bone marrow donors were of the *BL6* background, whose bone marrow did not lead to a graft vs. host response in irradiated *FVB* mice. Myc-CaP cells derived from the *FVB* background were provided by C. Sawyers (UCLA and Memorial Sloan Kettering Cancer Center)[6] and were cultured under standard conditions and confirmed to be mycoplasma free. Myc-CaP cells were injected subcutaneously into the flank of male *FVB* mice as described[6]. Tumor growth was measured with a caliper. Surgical procedures were as described[6].

Human specimens

Anonymous human prostate, benign prostatic hyperplasia and prostate cancer frozen sections were provided by the Cooperative Human Tissue Network (CHTN). Pathology reports were provided by CHTN for each sample.

CXCL13 and B cell depletion and LT inhibition

CXCL13 neutralizing antibody was purchased from R&D and administered i.p. at 200 mg/mouse as described[7]. Anti-CD20 was kindly provided by Genentech (Oceanside, CA) and was administered i.p. at 250 μg/mouse. LTβR-Ig fusion protein was a kind gift from Yang-Xin Fu (University of Chicago, Chicago, IL) and was administered as described[8]. hIgG and mouse IgG2a were purchased from Sigma-Aldrich and were used as controls.

IKKβ inhibitors

ML120 was kindly provided by Millenium Inc. and administered orally as described[9]. IKKβ Inhibitor IV was purchased from Calbiochem and was tail vein injected as described[10].

Histological procedures

Mouse prostate and CaP tissues and dissected metastatic tumors were immersed in 10% neutral buffered formalin before sectioning and paraffin embedding. Sections were stained and processed as described[11], using H&E stain, TUNEL assay kit or antibodies for IKKα (Imgenex), phospho-STAT3 (Cell Signaling) and CD19 (eBioscience) as described[12]. Frozen sections of human and mouse origins were fixed in acetone and processed as described [11], using antibodies for AR (Santa Cruz), B220 (BD),CD20 (BD), CD4 (BD) and CD8 (BD).

Analysis of RNA and protein expression

Total tissue RNA was prepared using RNAeasy (Qiagen). Quantitative PCR was performed as described[12]. Cells and tumors were lysed and analyzed by SDS-polyacrylamide gel electrophoresis and immunoblotting[12] with antibodies to histone H3, α-tubulin, STAT3 (Santa Cruz Biotechnology), ERK, phospho-ERK, AKT, phospho-AKT, phospho-STAT3 (Cell Signaling). Nuclear extracts were prepared and analyzed for NF-κB DNA-binding as described[13].

Lentiviral and retroviral transduction

siRNAs to mouse IKKα, IKKβ and LTβR mRNAs were cloned into pLSLPw, provided by I. Verma (The Salk Institute), and lentivirus stocks were prepared as described[11]. Virus-containing supernatants were added to myc-CaP cells for 2 days with polybrene, and transduced cells were selected in 5 μg ml^{-1} puromycin (Invitrogen).

Leukocytes purification and flow cytometry

Peripheral blood mononuclear cells (PBMCs) were isolated by centrifugation on a double-layered Histopaque-Ficoll (GE Lifescience) gradient. Splenic B and T lymphocytes were isolated by magnetic cell sorting (MACS) with CD4, CD8 or CD19 antibodies conjugated to magnetic beads. Tumor infiltrating leukocytes were stained with CD45, B220, LTβR-Ig, TCRβ, Gr1, CD4 and CD8 fluorescent antibodies, as well as Aqua LIVE/DEAD dye (Molecular Probes) and analyzed on a flow cytometer (Accuri C6 or Becton Dickinson LSR II).

Statistical analyses

Results are expressed as means $\pm$ s.e.m. or s.d. Data were analyzed by Student's t-test and Kaplan-Meier survival analysis using GraphPad Prism statistical program. Error bars depict s.e.m. or s.d. P values >0.05 were considered insignificant (ns), 0.01 to 0.05 were considered significant (*), 0.001 to 0.01 were considered very significant (**) and < 0.001 were considered as highly significant (***).

REFERENCES:

1 Greenberg, N. M. *et al.* Prostate cancer in a transgenic mouse. *Proceedings of the National Academy of Sciences of the United States of America* **92**, 3439-3443, (1995).

2 Wu, X. *et al.* Generation of a prostate epithelial cell-specific Cre transgenic mouse model for tissue-specific gene ablation. *Mechanisms of development* **101**, 61-69, (2001).

3 Kuhn, R., Schwenk, F., Aguet, M. & Rajewsky, K. Inducible gene targeting in mice. *Science* **269**, 1427-1429, (1995).

4 Tumanov, A. V. *et al.* Dissecting the role of lymphotoxin in lymphoid organs by conditional targeting. *Immunol Rev* **195**, 106-116, (2003).

5 Kim, S. *et al.* Carcinoma-produced factors activate myeloid cells through TLR2 to stimulate metastasis. *Nature* **457**, 102-106, (2009).

[6] Watson, P. A. *et al.* Context-dependent hormone-refractory progression revealed through characterization of a novel murine prostate cancer cell line. *Cancer research* **65**, 11565-11571, (2005).

[7] Zheng, B. *et al.* CXCL13 neutralization reduces the severity of collagen-induced arthritis. *Arthritis and rheumatism* **52**, 620-626, (2005).

[8] Lee, Y. *et al.* Recruitment and activation of naive T cells in the islets by lymphotoxin beta receptor-dependent tertiary lymphoid structure. *Immunity* **25**, 499-509, (2006).

[9] Izmailova, E. S. *et al.* Use of molecular imaging to quantify response to IKK-2 inhibitor treatment in murine arthritis. *Arthritis and rheumatism* **56**, 117-128, (2007).

[10] Park, B. K. *et al.* NF-kappaB in breast cancer cells promotes osteolytic bone metastasis by inducing osteoclastogenesis via GM-CSF. *Nature medicine* **13**, 62-69, (2007).

[11] Luo, J. L. *et al.* Nuclear cytokine activated IKKα controls prostate cancer metastasis by repressing maspin. *Nature* **446**, 690-694, (2007).

[12] Luo, J. L., Maeda, S., Hsu, L. C., Yagita, H. & Karin, M. Inhibition of NF-κB in cancer cells converts inflammation- induced tumor growth mediated by TNFα to TRAIL-mediated tumor regression. *Cancer cell* **6**, 297-305, (2004).

[13] Senftleben, U. *et al.* Activation by IKKα of a second, evolutionary conserved, NF-κB signaling pathway. *Science* **293**, 1495-1499, (2001).