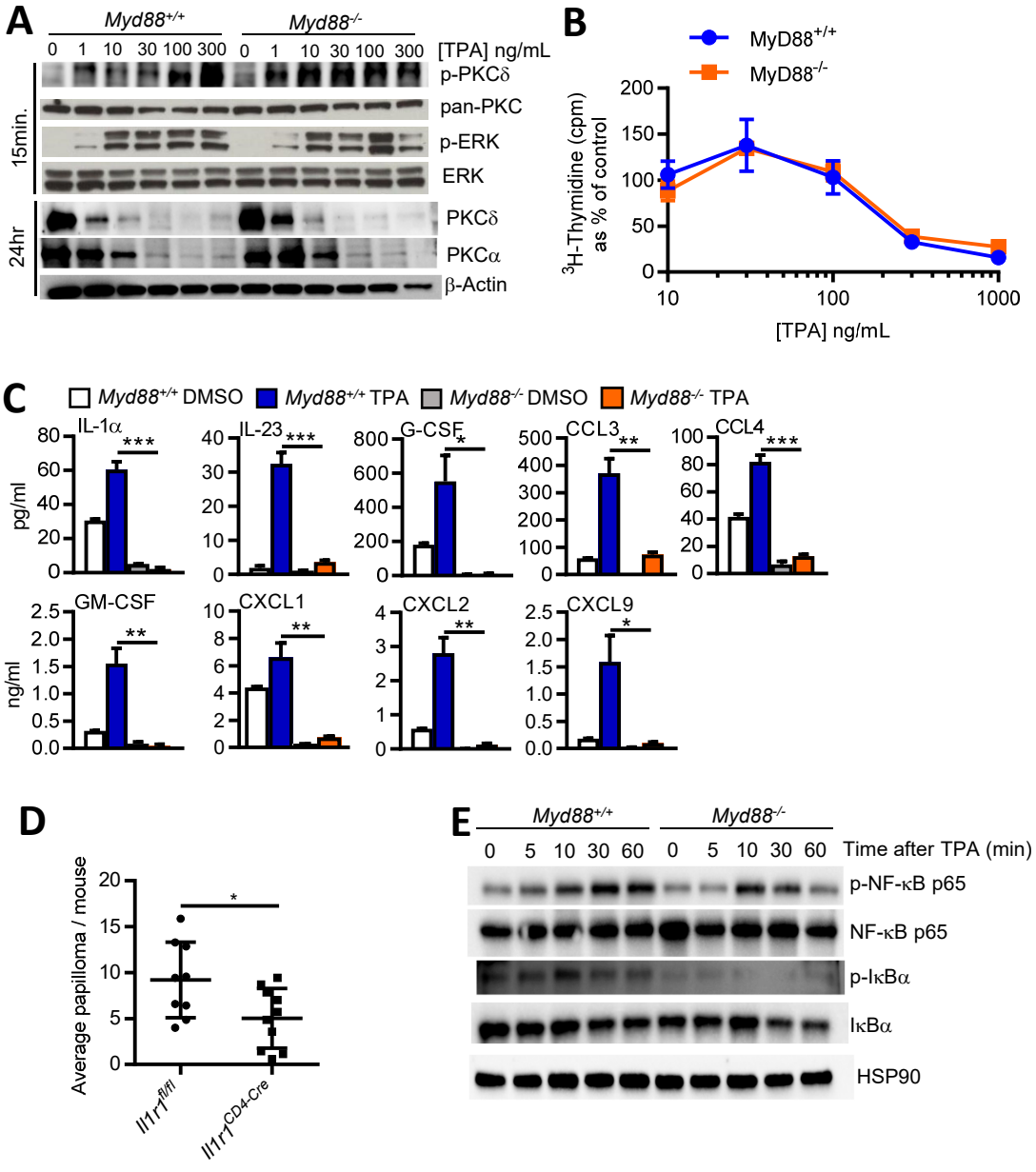
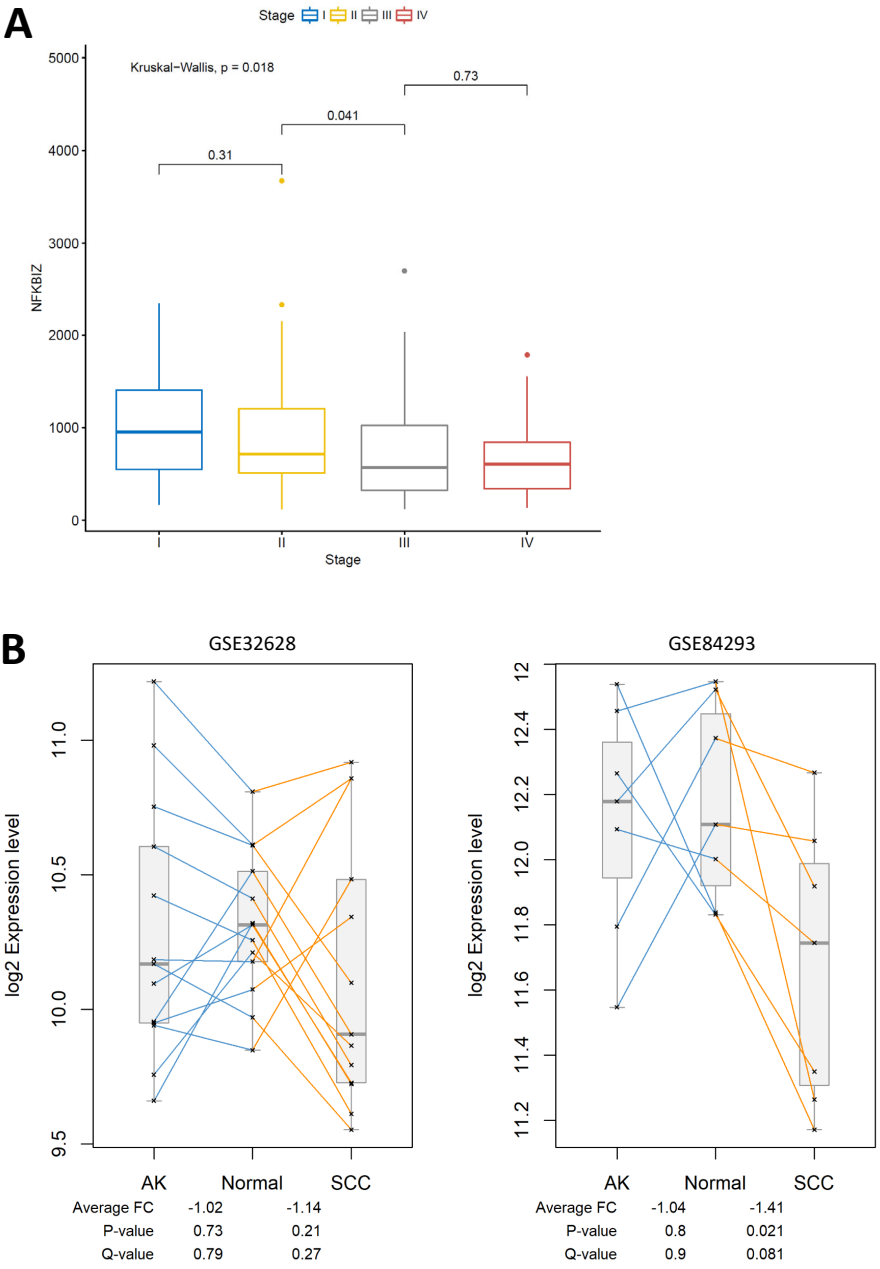
Supplemental figure 1: MyD88 deficiency diminishes the induction of pro-inflammatory factors in keratinocytes. (A) Immunoblotting of total cell extracts from cultured primary WT or MyD88$^{-/-}$ keratinocytes treated with indicated TPA doses for 15 minutes or 24 hours. p-, phosphorylated. (B) Tritiated thymidine incorporation was measured in WT or MyD88$^{-/-}$ keratinocyte cultures treated with TPA for 24 hours. Data shown are representative of two independent experiments, and bars represent the mean ± SEM value of four replicates. (C) Cytokine and chemokine concentrations (ELISA) in culture supernatants from WT and MyD88$^{-/-}$ collected 24h after DMSO or TPA treatment. (D) Deletion of IL-1R in T cells (CD4-cre^{+}/Il1r1$^{fl/fl}$ mice) reduces the yield of tumors in DMBA/TPA treated mice. Plot represent the mean number of skin tumors per mouse (mean ± SEM) at week 20 post-initiation. Mice were treated with DMBA/0.2 mL acetone at time 0 then with 10 nmol TPA/0.2 mL acetone twice a week for up to 20 wk. *Il1r1$^{fl/fl}$* (n = 9), *Il1r1$^{CD4\text{-}Cre}$* (n= 10), * $P < 0.05$. (E) Immunoblotting of total cell extracts from primary WT or MyD88$^{-/-}$ keratinocytes treated with TPA for the indicated period. HSP90, heat shock protein 90.



Supplemental figure 2: *NFKBIZ* expression in colon adenocarcinoma according to stage (A) and expression in cutaneous SCC, normal skin (NS) and actinic keratoses (AK) from GSE 32628 and GSE84293 (B).



Footnote: GSE32628 is from Hameetman L, Commandeur S, Bavinck JN, Wisgerhof HC *et al*. Molecular profiling of cutaneous squamous cell carcinomas and actinic keratoses from organ transplant recipients. BMC Cancer 2013 Feb 5;13:58. PMID: 23379751. GSE84293 is from Chitsazzadeh V, Coarfa C, Drummond JA, Nguyen T *et al*. Cross-species identification of genomic drivers of squamous cell carcinoma development across preneoplastic intermediates. Nat Commun 2016 Aug 30;7:12601. PMID: 27574101

Supplemental figure 3: Schematic depiction of tissue autonomous and systemic contributions for the development of squamous skin tumors. It is well known that initiation of keratinocytes through *Hras* mutations is not sufficient to evoke tumor formation in the context of the intact skin environment. The current study reveals how signaling through NF-kB in multiple compartments amplifies the elaboration of factors required for a tumor promoting environment. We now show that the release of NF-kB dependent cytokines and chemokines from RAS initiated keratinocytes combined with similar factors released by TPA treated normal keratinocytes is not sufficient for tumor eruption in the absence of host-derived IL-17. Factors released by RAS initiated keratinocytes and TPA treated normal keratinocytes, and particularly IL-1α, attract and polarize IL-17 producing T cells to the skin through a NF-kB dependent process. The release of IL-17 in the tumor microenvironment and its action on both normal and initiated keratinocytes (depicted in red as RAS* and light grey as normal) provides sufficient signal amplification to fully evoke tumor emergence and growth. While NF-kB is required for every step in the process, it appears that oncogenic RAS, TPA and IL-17 signaling through IkBz provide crucial selection for expression of pro-tumorigenic molecules from each contributing cell type.