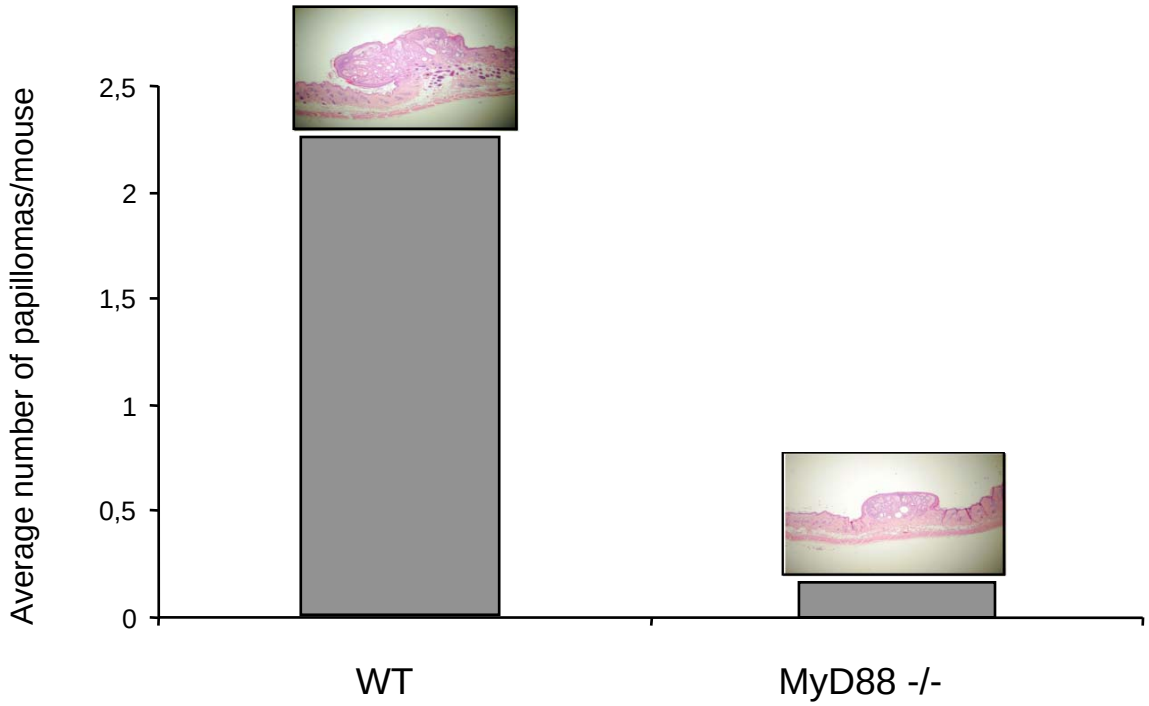
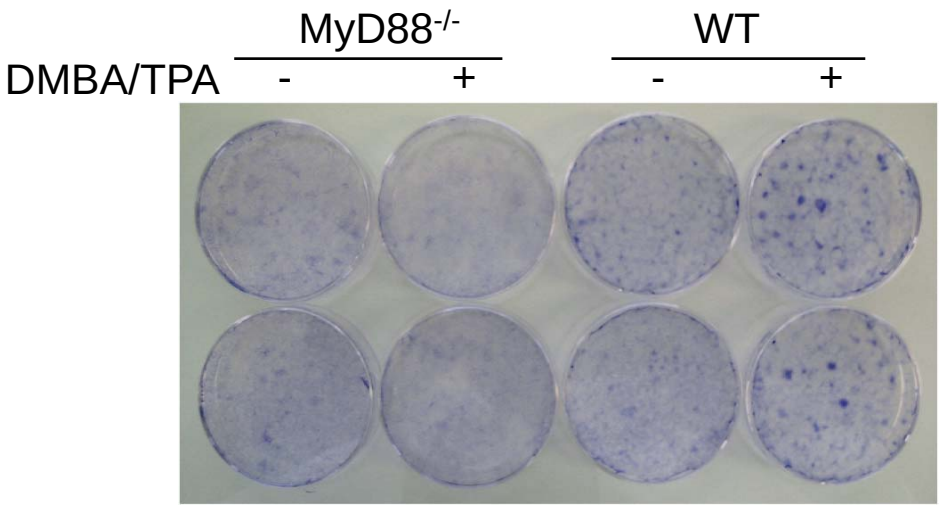
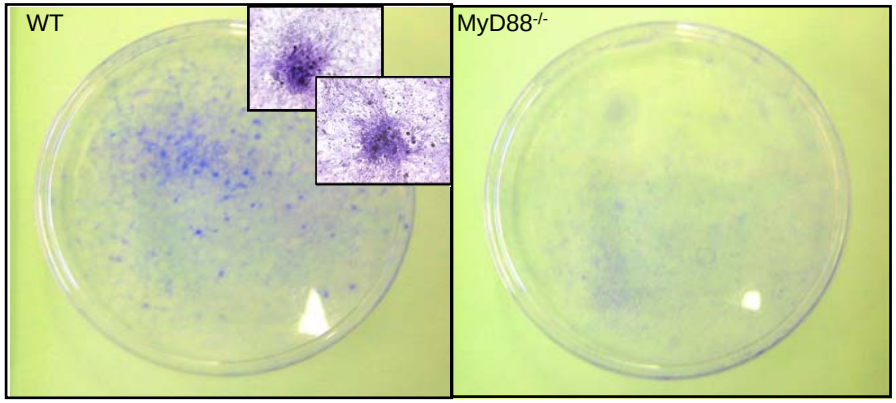



Supplementary Figure 1: Average number of skin papillomas/mouse in 8-week old wild-type (WT) and MyD88-/- mice (n = 20 per group) subjected to a two-stage carcinogenesis protocol using DMBA and TPA.
Insets with representative papilloma sections show well-developed, advanced-stage papillomas in the WT group, and smaller, less-advanced lesions in the few papillomas that develop in MyD88-/- mice.

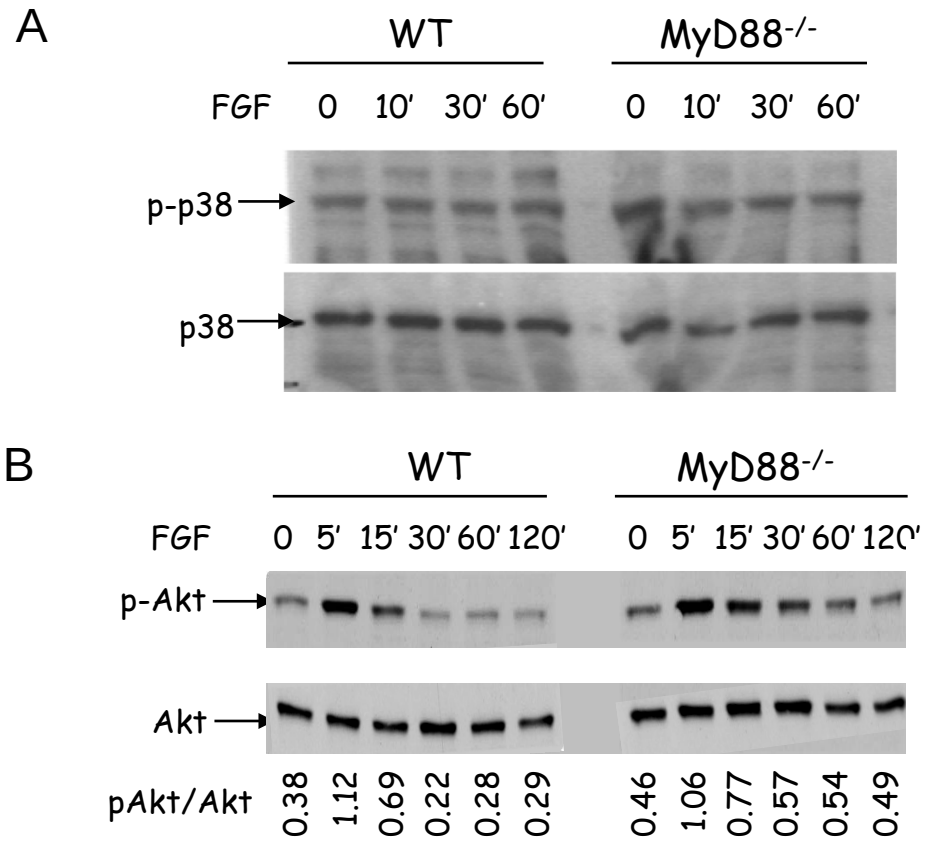
A



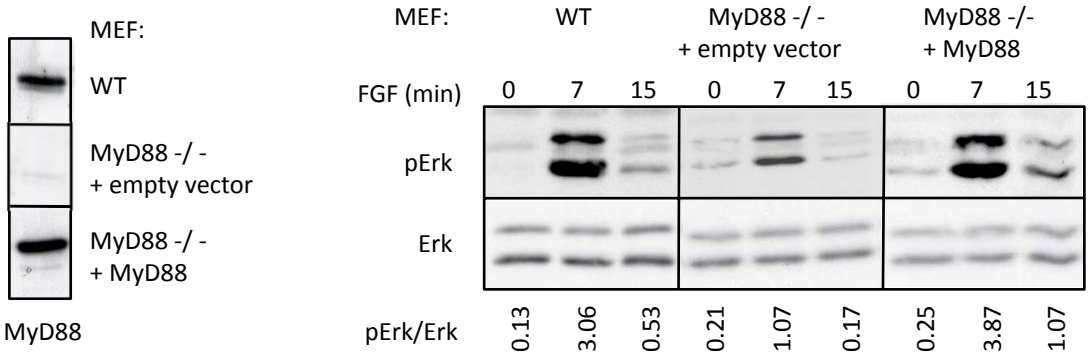

B



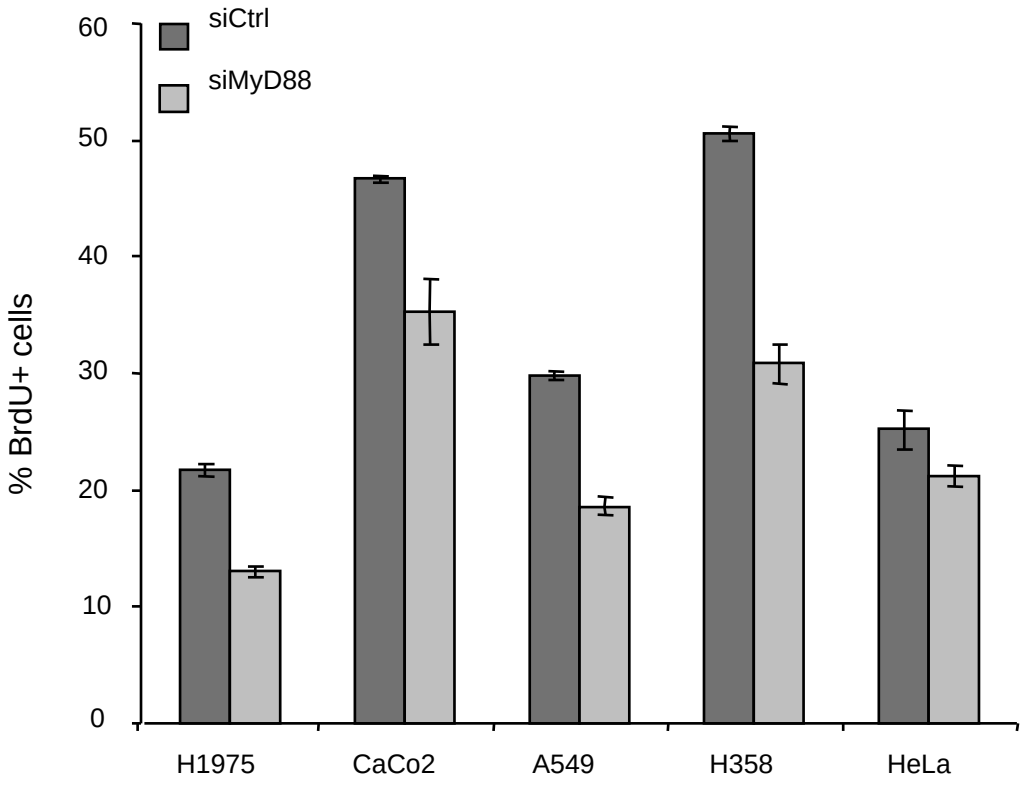

Supplementary Figure 2: (A) Wild-type and MyD88-/- MEFs were treated or not in duplicate with DMBA then twice a week with TPA. Cells were fixed and stained with crystal violet. (B) Example of focus formation induced by Rasv12 and Myc in primary embryonic fibroblasts isolated from WT and MyD88-/- mice. Inset shows larger magnification (10X) of morphological foci present in WT, but not in MyD88 MEFs.



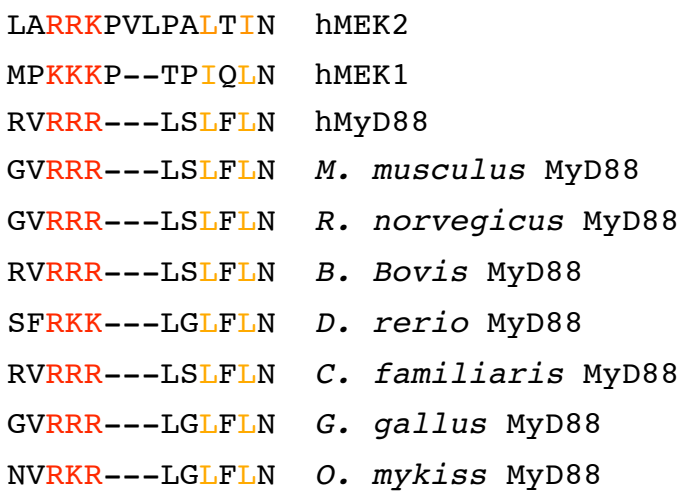

Supplementary Figure 3: Neither p38 nor Akt require MyD88 for their phosphorylation following Ras signalling. Primary MEFs were starved overnight, then treated with FGF8b for the indicated times. Phosphorylated and total p38 (A) and Akt (B) were then evaluated by western blot using specific antibodies.



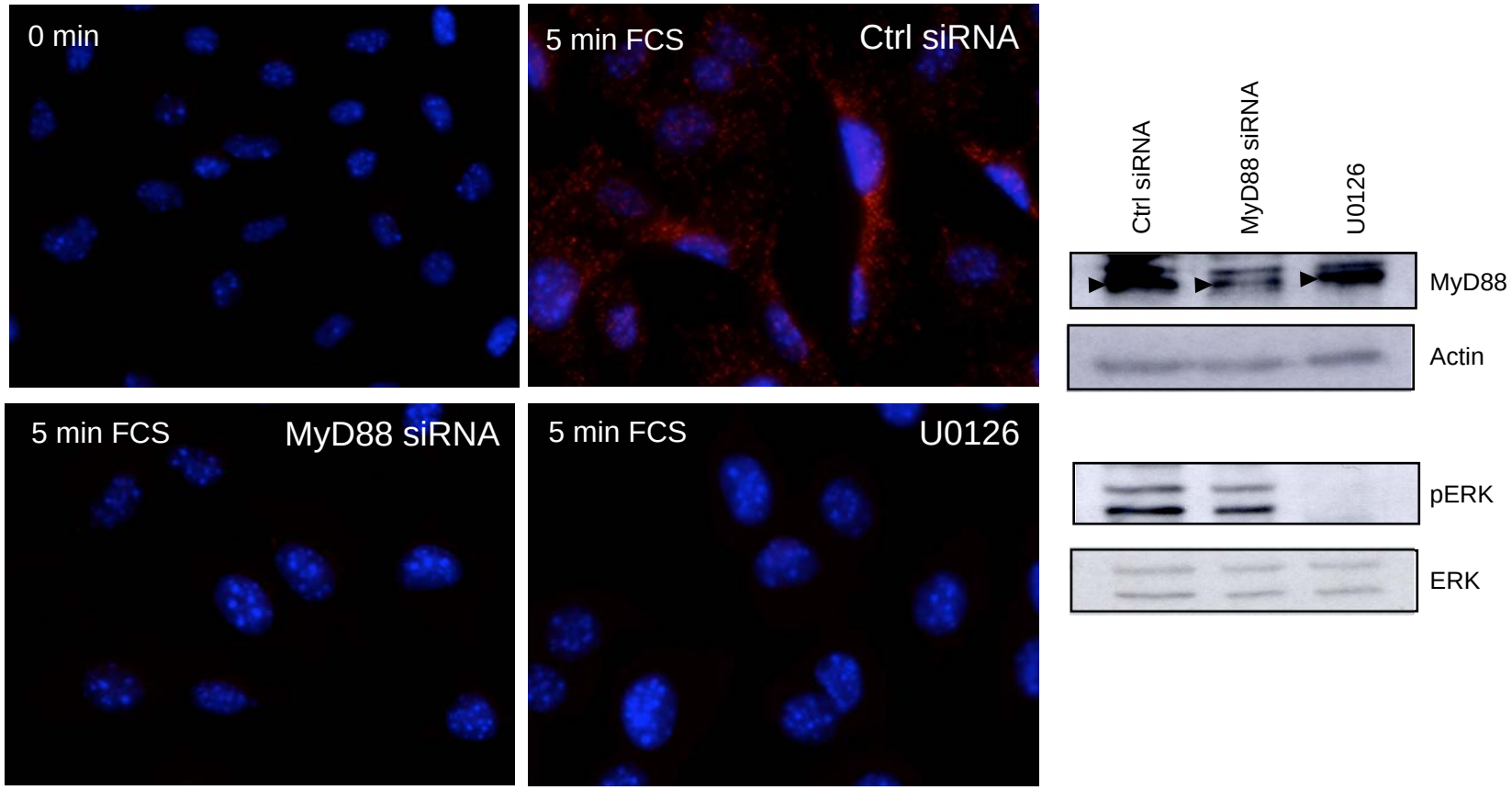

Supplementary Figure 4 : Serum-starved wild-type MEFs (WT) or MyD88$^{-/-}$ MEFs that were retrovirally-reconstituted with MyD88 or that were transduced with an empty vector, were treated with FGF for the indicated times. Western blots show reconstitution efficiency (MyD88), Erk phosphorylation (pErk), and total Erk (Erk).



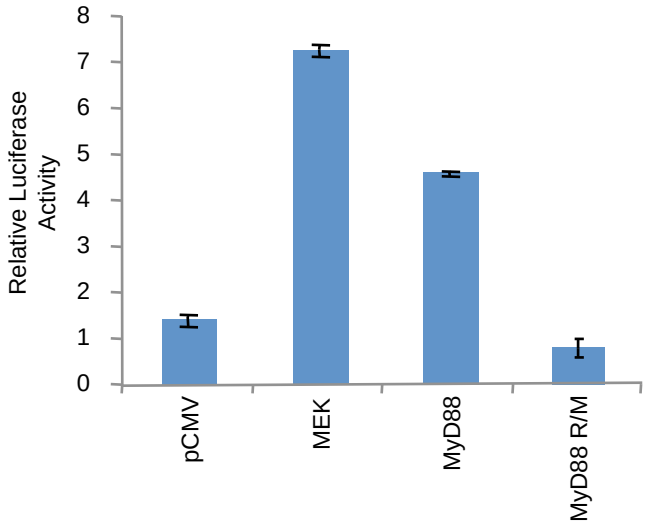

Supplementary Figure 5: Decreased proliferation of human cell lines upon treatment with MyD88 siRNA. Indicated human cell lines were transfected for 48 hours with control (siCtrl) or MyD88-specific siRNA (siMyD88), pulsed with bromodeoxyuridine (BrdU), then analysed by flow cytometry. Results are expressed as percentage of cells incorporating BrdU after a 1-hour pulse. Bars represent standard error.



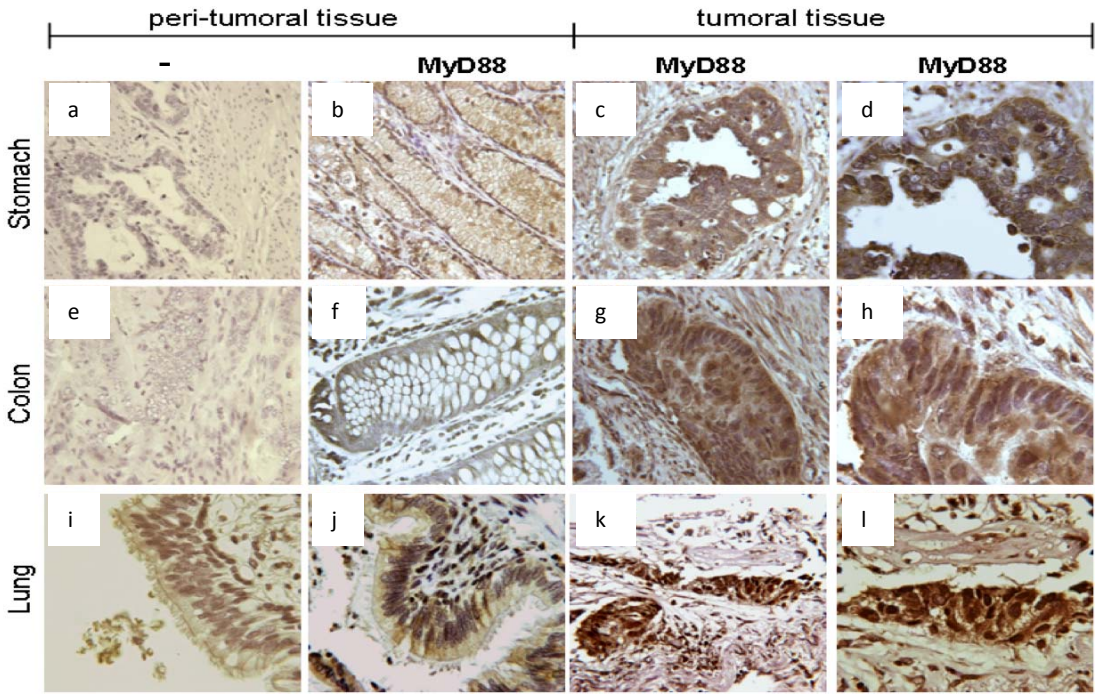

Supplementary Figure 6: Amino acid alignment showing that MyD88 contains an evolutionarily conserved Erk docking motif that is present in the MEK1 and MEK2 MAPKKs.



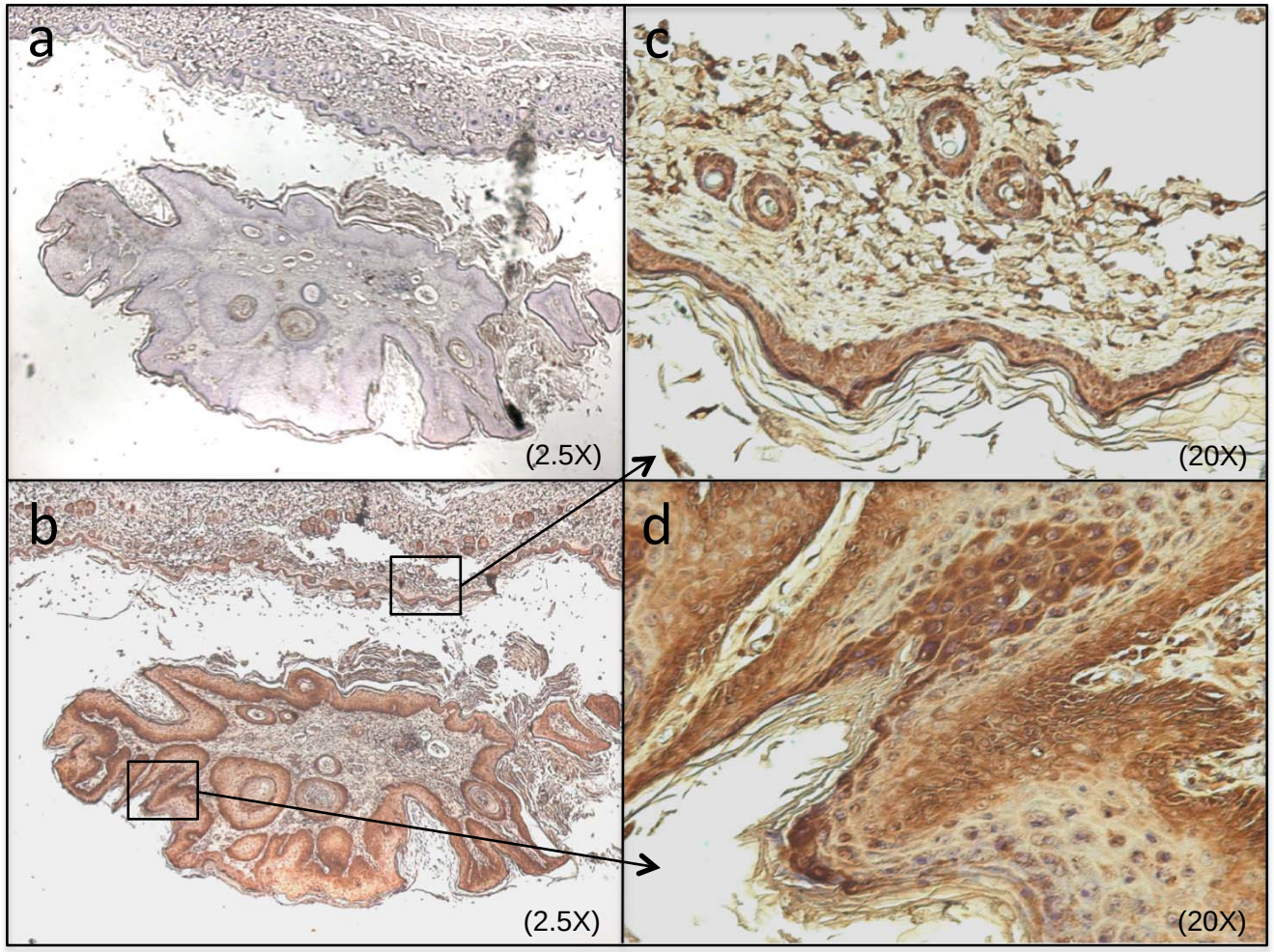

Supplementary Figure 7: Controls for the interaction between endogenous MyD88 and phosphoErk upon cell activation revealed by proximity ligation assay (red dots). B16F10 melanoma cells were transfected with control or MyD88-specific siRNA, or treated with U0126. They were then starved and activated with FCS for 5 minutes. Cells were stained with antibodies to MyD88 and phosphor-Erk followed by the appropriate DNA-linked secondary antibodies according to the Duolink® protocol. Western blot shows the corresponding MyD88 (arrowheads) and pErk extinction.



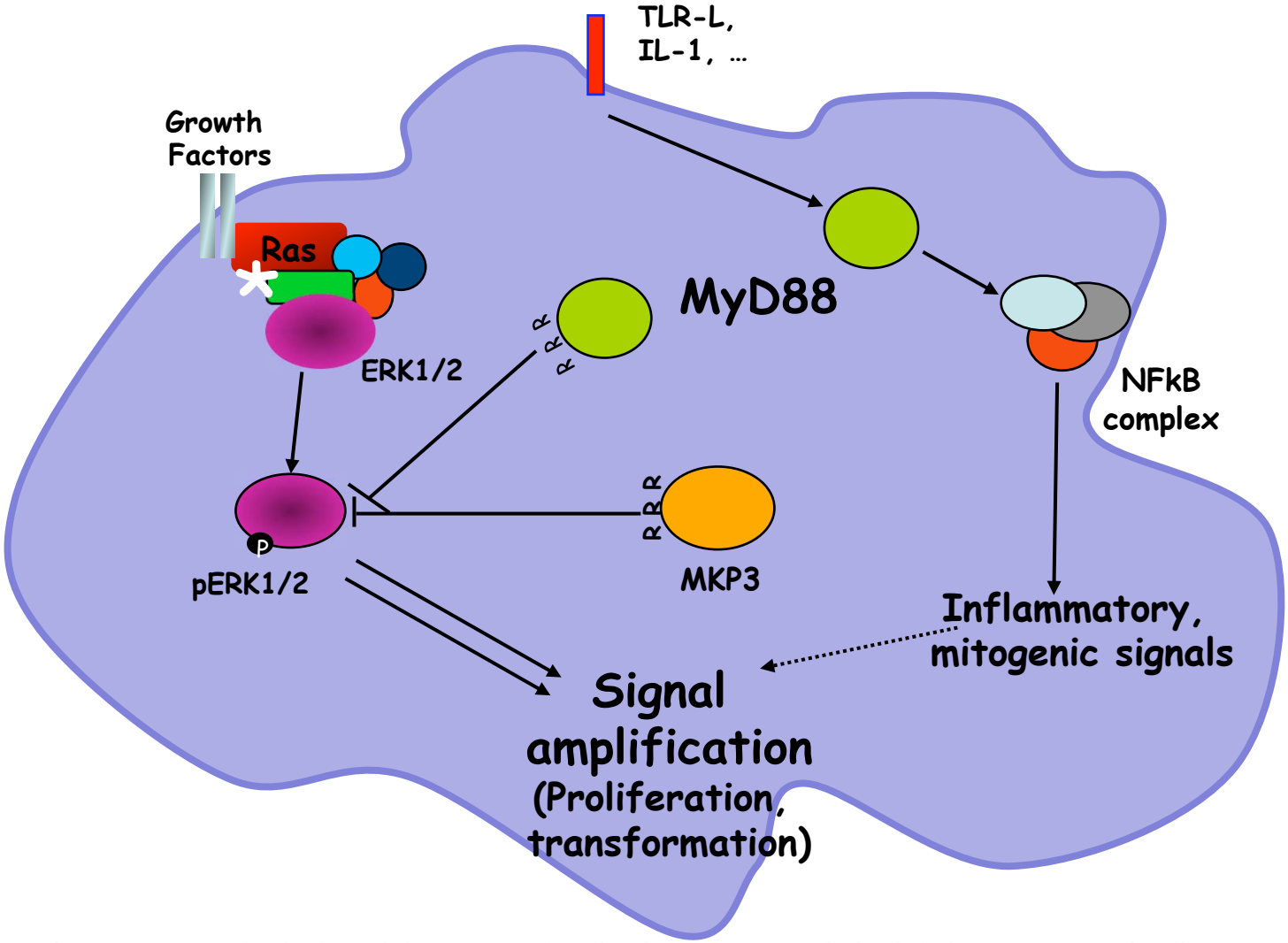

Supplementary Figure 8: Wild-type MyD88, but not a mutant unable to interact with Erk (MyD88 R/M) can activate the canonical MAPK pathway. MEK, MyD88, MyD88 R/M, or control plasmid were transfected in triplicate into HeLa cells. Luciferase activity from an Elk-luciferase reporter plasmid was quantitated 24h later. Values were normalized based on Renilla luminscence.




Supplementary Figure 9: MyD88 is overexpressed in cancer tissue. MyD88 immunohistochemical staining of human stomach (a–d), colon (e–h) and lung (i-l) sections. (b, f, j) peri-tumoral, normal epithelium. (c, g, k) tumors at 20X magnification. (d, h, l) tumors at 50X magnification. (a, e, i) peri-tumoral with secondary antibodies only.




Supplementary Figure 10: MyD88 is overexpressed in DMBA/TPA-induced papillomas in mice. MyD88 immunohistochemical staining of whole papilloma (b), normal skin epithelial lining (c), and tumoral tissue (d). (a) whole papilloma stained with secondary antibody alone.




Supplementary Figure 11: Hypothetical model of MyD88 implication in cancer via both inflammatory and cell autonomous mechanisms.

In response to growth factors or oncogenic signalling, Erk is phosphorylated then rapidly dephosphorylated by MKP3. MyD88 binds to pErk via its D-domain, thereby preventing the pErk-MKP3 interaction via the same motif and maintaining Erk in a active, phophorylated state for a longer period of time. At the same time, MyD88 allows the activation of NFkB by soluble mediators (e.g. IL-1), leading to the activation of further inflammatory and mitogenic signals. This combination of MyD88-dependent signals leads to enhanced cell activation, proliferation, and eventually, transformation.