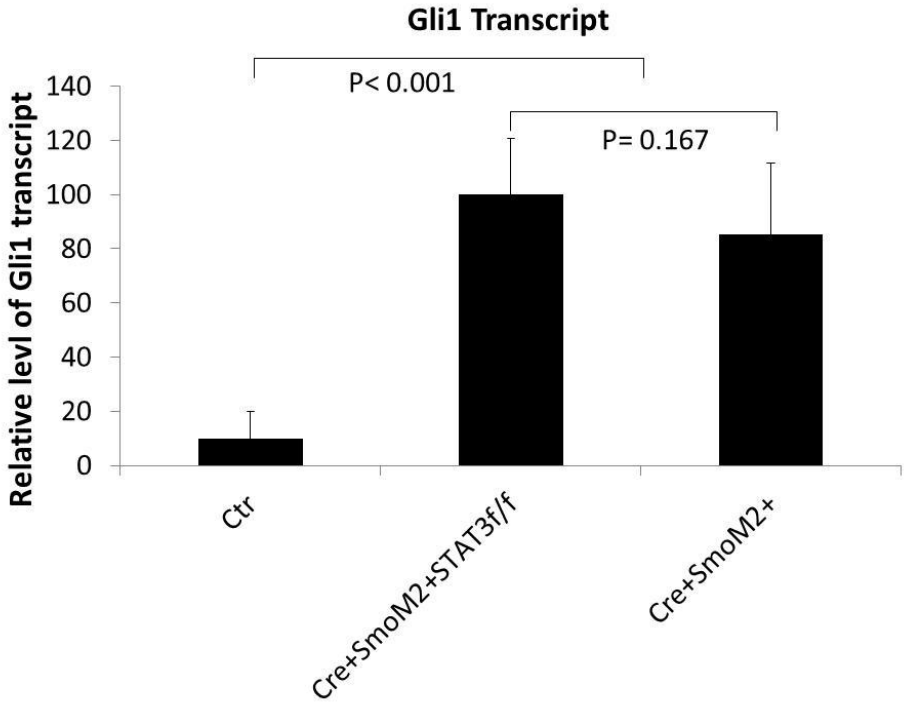
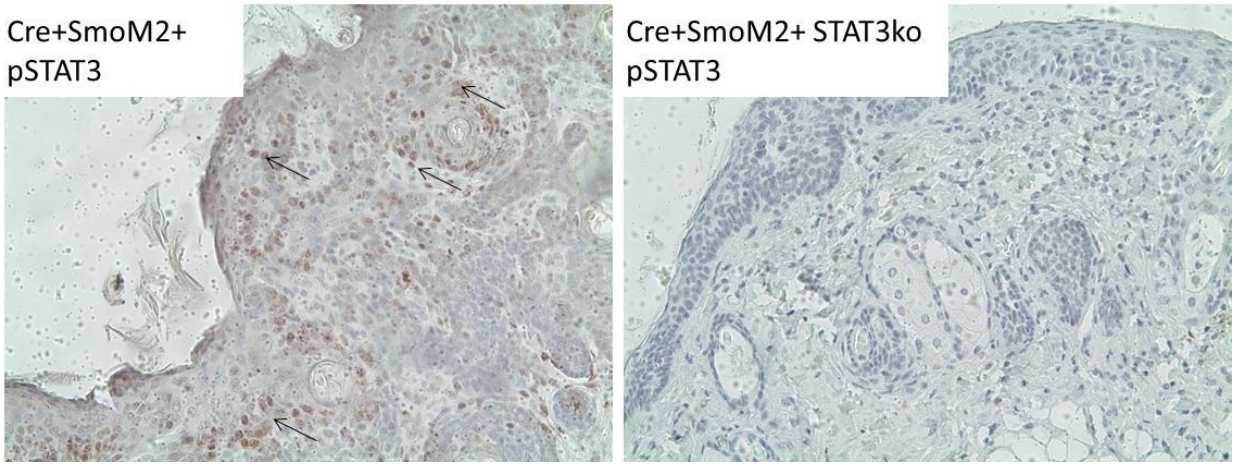
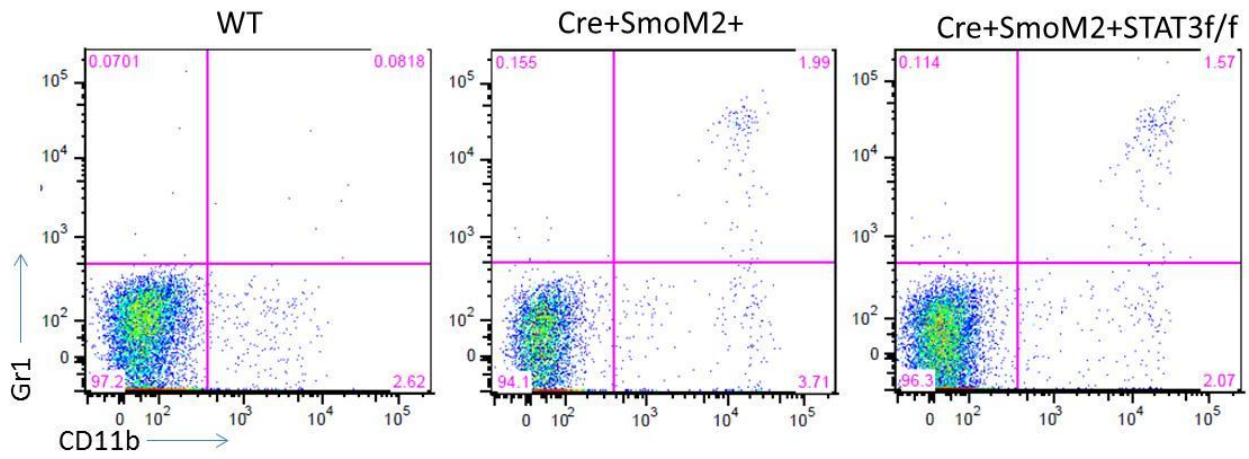
SUPPLEMENTARY FIGURES



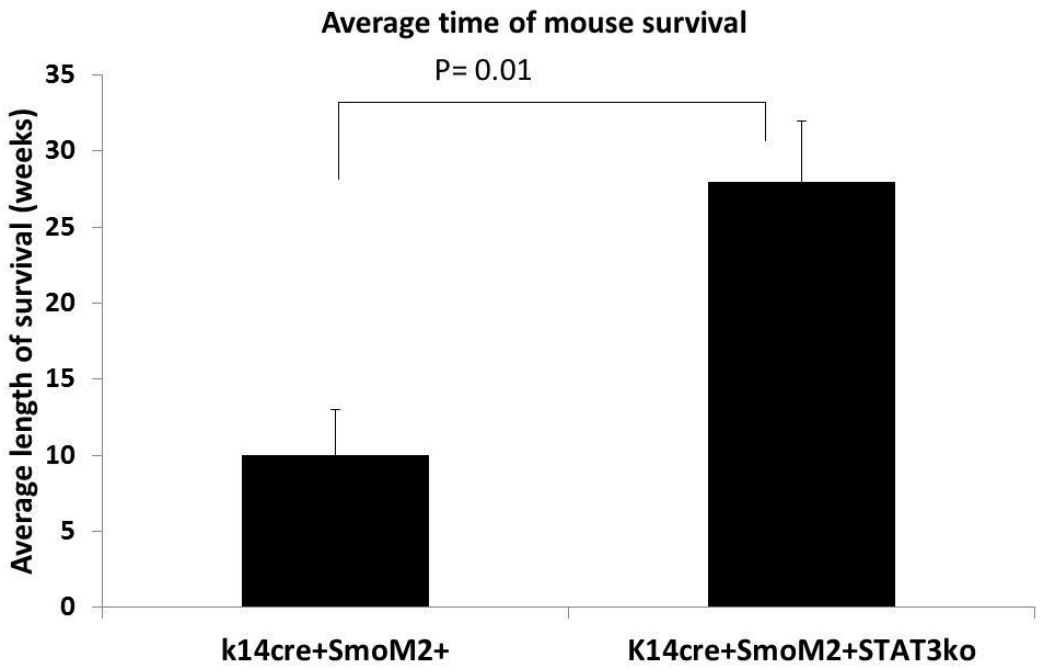
Supplementary Figure 1- Gli1 expression in epidermis from wt (indicated as ctr), K14cre^{+} SmoM2^{+} (as Cre+SmoM2+) and K14cre^{+}SmoM2^{+}STAT3$^{f/f}$(Cre+SmoM2+STAT3f/f) mice. Quantitative Real-time was used to detect the level of Gli1 transcript from total RNAs of epidermis. Triplicates from each sample were used, and each group had more than 3 samples. The level of keratin 14 was used as the internal control. P value <0.05 was regarded as statistical significance (two tailed *t* test). While expression of SmoM2, regardless of STAT3 k/o, resulted in a statistically significant increase of Gli1 (p value <0.001), STAT3 k/o had no significant effects on Hh target gene Gli1 expression (p value =0.167).



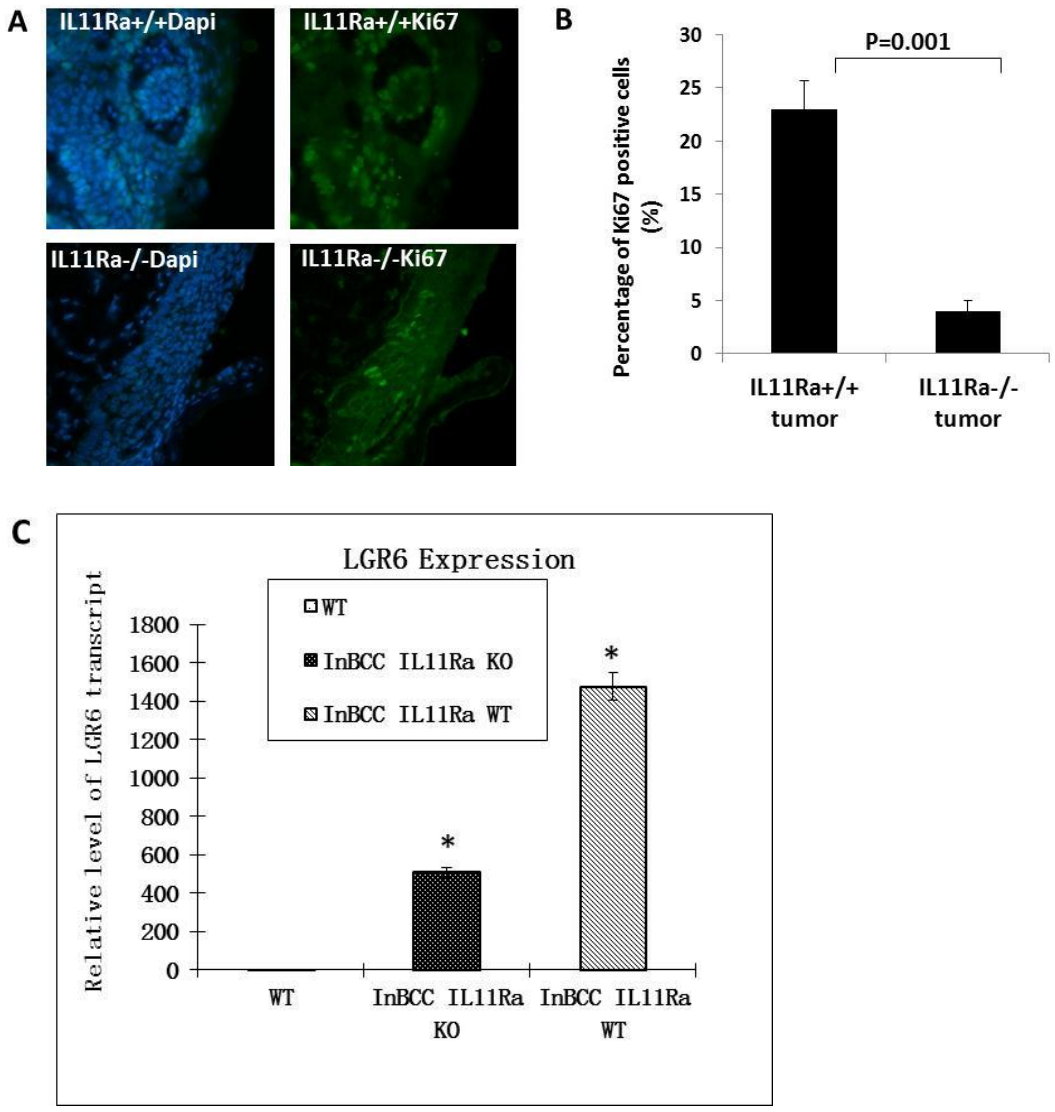
Supplementary Figure 2- Detection of pSTAT3 in skin tissues. Skin tissues from Cre+SmoM2+ or Cre+SmoM2+STAT3f/f mice were fixed in formalin, paraffin-embedded, and sectioned at 5mm. IHC was performed using specific pSTAT3-Y^{705} antibodies. Positive staining in brown (indicated by arrows) was noticeable in nucleus of Cre+SmoM2+ tissues, not Cre+SmoM2+ STAT3-k/o tissues, indicating complete knockout of STAT3 signaling in the epidermis of Cre+SmoM2+STAT3-k/o mice.



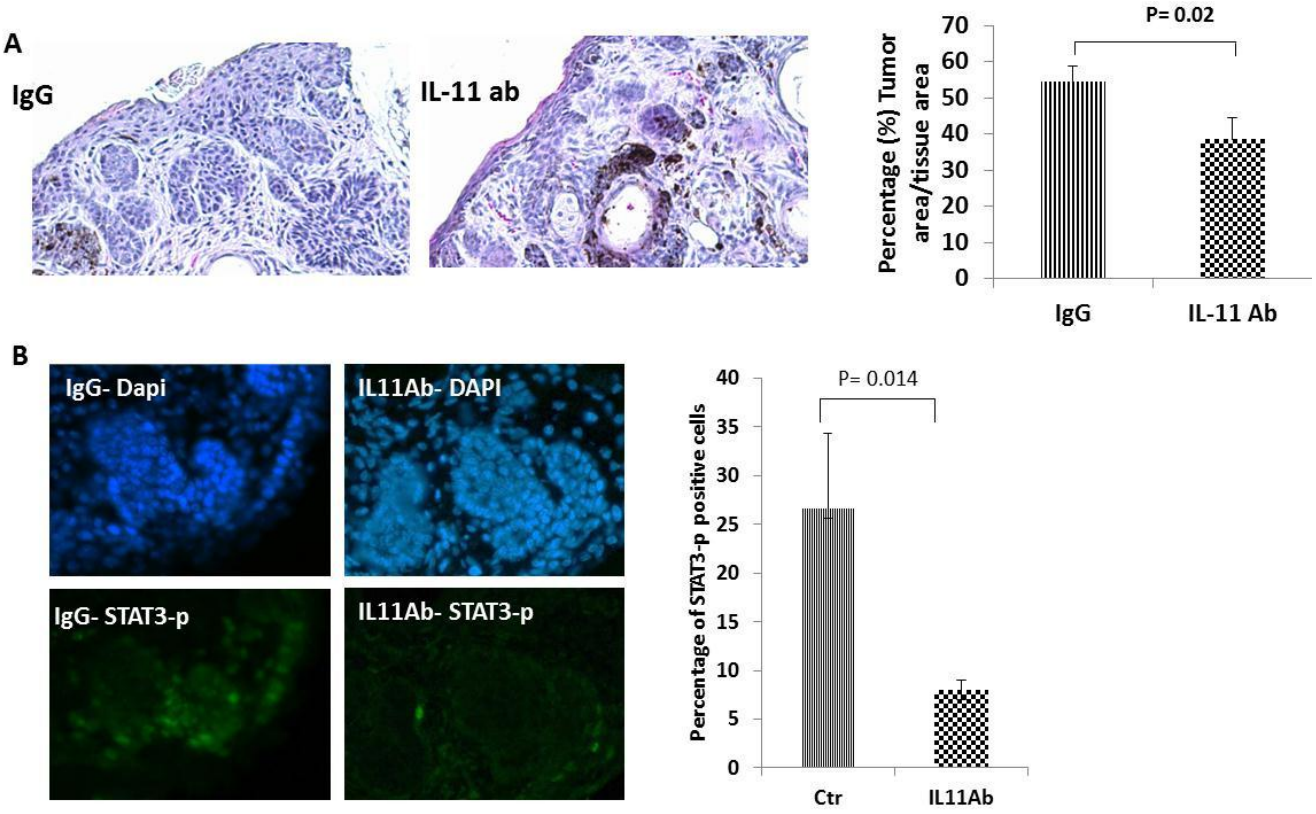
Supplementary Figure 3- Detection of myeloid derived cells in skin tissues Cell surface expression of CD11b and Gr1 were used to evaluate myeloid derived cells. Myeloid-derived cells were not detectable in normal mouse skin, but were over 1% of the total cell population in tumor-bearing mice. This population did not change much after STAT3 knockout in epidermis, indicating that epidermal STAT3 signaling does not affect the population of myeloid-derived cells.



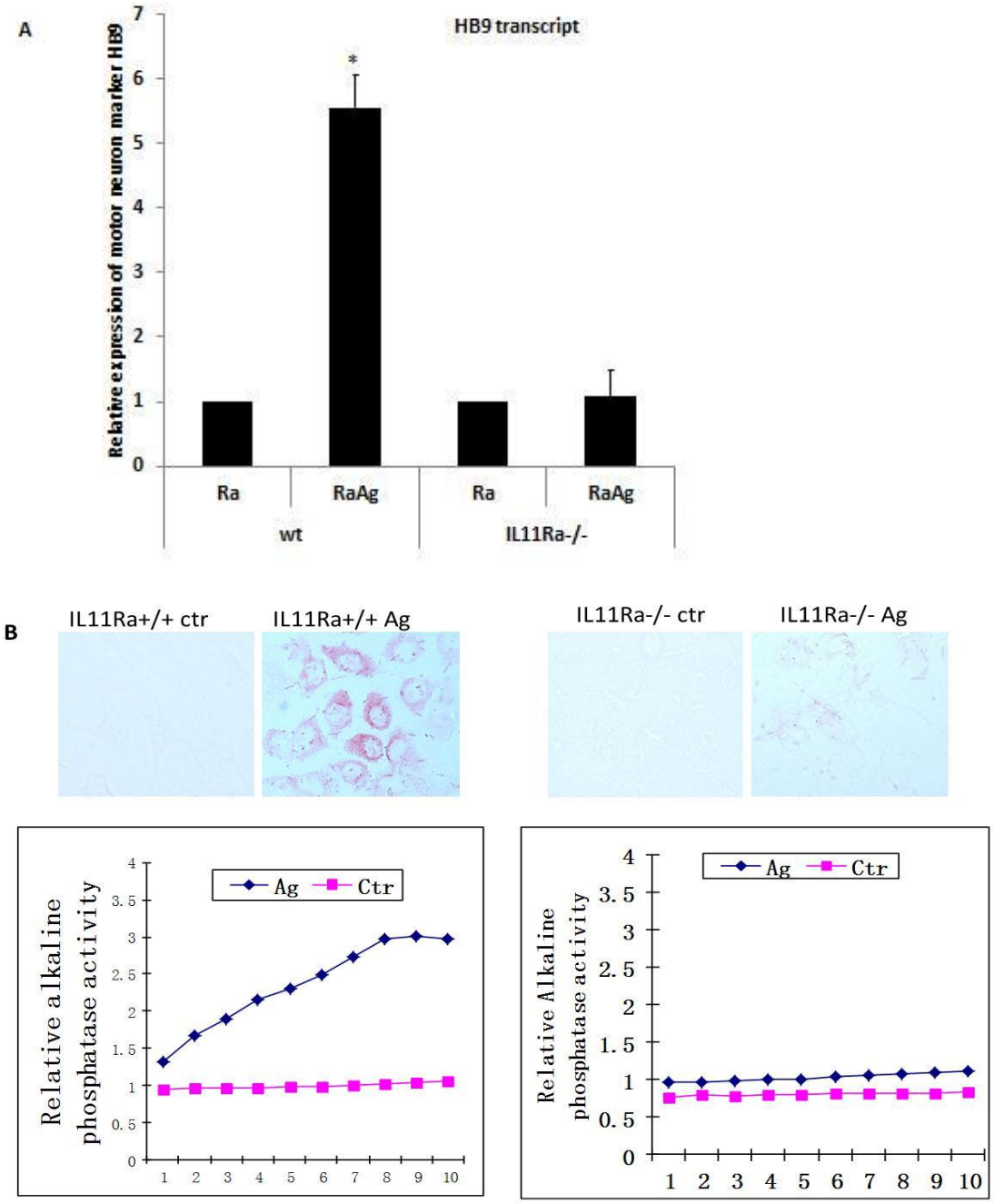
Supplementary Figure 4- Survival of tumor bearing mice. Mice with different genotypes were followed for eight months to assess animal survival. This figure is a data summary from over 20 mice. While the average survival time of tumor bearing K14cre+SmoM2+ mice is 10 weeks, K14cre+SmoM2+ STAT3 k/o mice can survive more than six months.



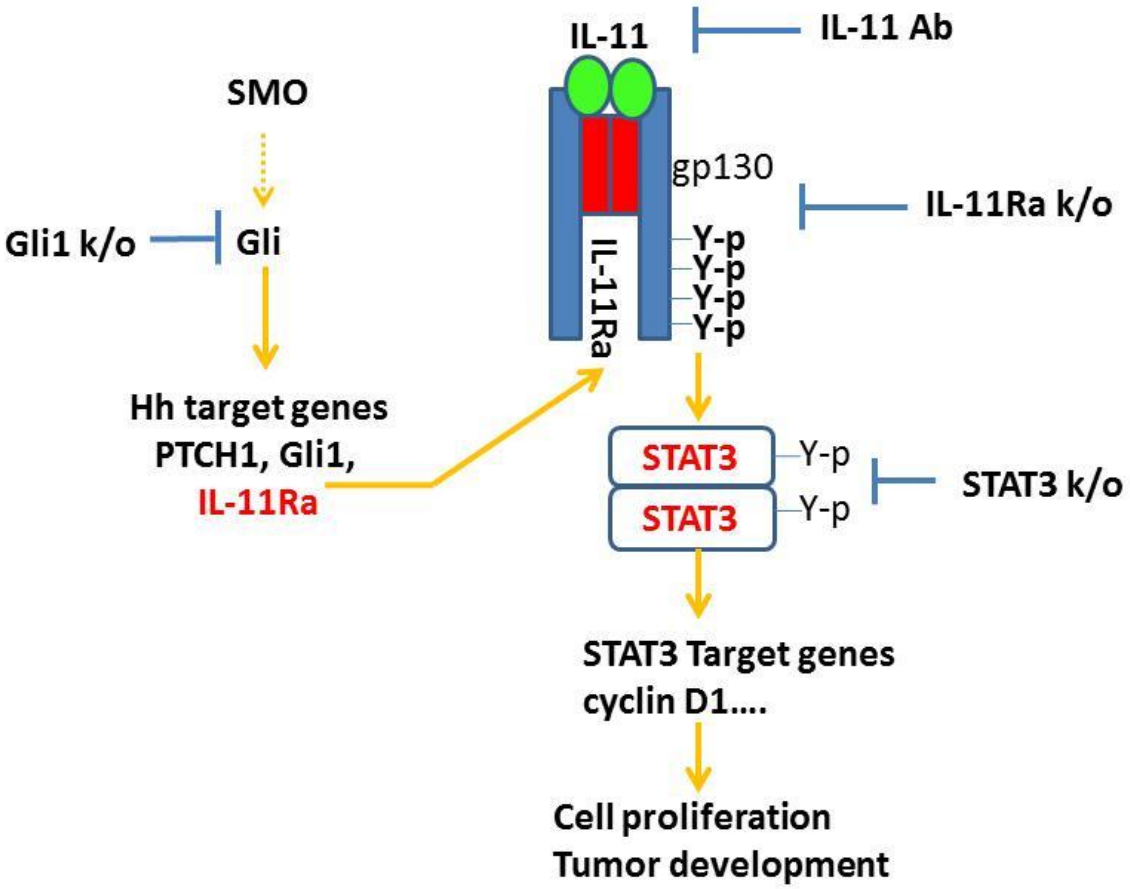
Supplementary Figure 5- Effects of IL-11Rα knockout on cell proliferation and LGR6 expression. The percentage of Ki67 positive staining (Ki67 positive cells vs DAPI positive cells) in skin tissues was used to indicate cell proliferation. Ki67 positive cells were in green (as indicated in **A**). Eight areas of skin from each mouse were used to calculate the percentage of ki67 positive cells, and at least 2 mice were used in each group for the measurement. The summary was shown in **B**. The level of LGR6 expression was measured by real-time PCR with GAPDH as the internal control. Student *t* test was used to obtain the p values between the groups, with p value<0.05 (indicated as * in **C** or shown in **B**) as statistically significant.



Supplementary Figure 6- Effects of IL-11 neutralizing antibodies on the tumor size and STAT3 phosphorylation. Following subcutaneous injection of IL-11 neutralizing antibodies or the control IgG, skin tissues were fixed for H&E staining for gene expression analyses. **A** shows typical H&E images (IgG as the control and IL-11ab as the neutralizing antibody treated group). The tumor size was measured by the percentage of tumor area in a given tissue area (8 areas in each mouse and at least 2 mice were used for the measurement). **B** shows expression of phosphorylated STAT3 (Y^{705}) in different tissues, and the percentage was calculated using the number of STAT3 phosphorylation positive cells in a given area (the total DAPI positive cells). Almost all the staining was in the nucleus. P values< 0.05 (students' *t* test) were statistically significant.



Supplementary Figure 7- Effects of IL-11Rα down-regulation on motor neuron differentiation and osteoblast differentiation. The procedures for these assays have been previously published (Fan et al, JBC 285: 36570-6, 2010). The level of HB9 transcript, which was detected by real-time PCR, was used to represent motor neuron differentiation (**A**). P values <0.05 are statistically significant (indicated by *). IL11Ra-/- indicates cells with down-regulation of IL11Rα. Ra indicates retinoic acid, and Ag indicates Smo agonist purmorphamine. Alkaline phosphatase was detected by direct staining with substrate (**B** up panel) or measurement of OD570nm over 100minutes (**B** bottom panel, in the x-axis, 1=10 minutes).



Supplementary figure 8- A model for Hh-mediated activation of STAT3 signaling. Based on our data, we propose that SmoM2 induces expression of IL-11Rα through downstream Gli1 transcription factors (Fig. 1G). Together with gp130, IL-11Ra increases signal transduction of IL-11, leading to elevated STAT3 signaling as indicated by STAT3 phosphorylation (Fig.2). Activation of STAT3 increases expression of cyclin D1 (Fig.6), cell proliferation (Fig.4), expansion of skin stem/progenitor cell population (Fig.5) and tumor development (Fig.2 and 3). The effect of Hh-mediated STAT3 signaling activation seems to be direct because addition of Smo agonist was sufficient to induce STAT3 phosphorylation (Fig.8). We have used several GEM to test this model. Disruption of the IL-11Rα/STAT3 signaling axis by either epidermal depletion of STAT3 (Fig.3), IL-11Rα gene knockout (Fig.7) or neutralizing antibodies to IL-11 (Supplementary Figure 6) all led to reduced cell proliferation and tumor size reduction. Similarly, down-regulation of IL-11Ra was sufficient to abolish Smo agonist-mediated STAT3 phosphorylation (Fig.8). Thus, our results support the hypothesis that the IL-11Rα/STAT3 signaling axis is critical for Hh-mediated cell functions and carcinogenesis.