

Figure S1 The expression pattern of the *Igf2bps* (Insulin-like growth factor 2 binding proteins), *Igfbps* (Insulin-like growth factor binding proteins) and *Igf2r* in mesenchymal cells.

A~I t-SNE plot showing the expression pattern of *Igf2bp1*, *Igf2bp2*, *Igf2bp3*, *Igfbp2*, *Igfbp3*, *Igfbp4*, *Igfbp5*, *Igfbp6* and *Igf2r* among mesenchymal cells.

Figure S2 Deletion of *Igf2* in pro-osteoblasts induces significant lower expression of *Igf2* and osteogenesis-related genes in CKO mice.

A RT-qPCR showing the relative expression of *Igf2* of BMSCs from *Osx^{Cre}* (Ctrl) and *Osx^{Cre}; Igf2^{fl/-}* (CKO) mice (n=3 per group).

B RT-qPCR showing the relative expression of *Colla1*, *Alp*, *Runx2*, *Sp7* and *Ocn* of BMSCs from *Osx^{Cre}* (Ctrl) and *Osx^{Cre}; Igf2^{fl/-}* (CKO) mice (n=3 per group).

Figure S3 Deletion of *Igf2* in pro-osteoblasts induces in structural deformities in craniofacial bones in CKO mice.

A Representative micro-CT images of mandibles and their magnifying views of the condyles from 12-wk-old male *Osx^{Cre}; Igf2^{fl/-}* (CKO) mice and littermate controls (Ctrl). Scale bar=2mm for left views and 500µm for magnified views.

B Representative micro-CT images of skulls from 12-wk-old male *Osx^{Cre}; Igf2^{fl/-}* (CKO) mice and littermate controls (Ctrl). The yellow arrows point to the structural deformities of the CKO mice. Scale bar=2mm.

Figure S4 The skeleton maldevelopment also exists in *Osx^{Cre}; Igf2^{fl/-}* mice in earlier developmental stage.

A Representative micro-CT images of femur and its magnifying views of the femur sections from 4-wk-old male *Osx^{Cre}; Igf2^{fl/-}* mice and littermate controls. Scale bar=1mm.

B Statical analysis of micro-CT of trabecular bone volume ratio (BV/TV), trabecular thickness (Tb. Th), trabecular number (Tb. N) and trabecular spacing (Tb. Sp) (n=4 per genotype).

C Representative micro-CT images of skulls from 4-wk-old male *Osx^{Cre}; Igf2^{fl/-}* (CKO) mice and littermate controls (Ctrl). The yellow arrow points to the structural deformities of the CKO mice. Scale bar=2mm.

D Statical analysis of micro-CT of cortical bone volume ratio (BV/TV) in C (n=3 per genotype).

E Representative H&E and Masson trichrome staining images of the femur sections from 2-wk&4-wk-old male *Osx^{Cre}; Igf2^{fl/-}* mice and littermate controls. Scale bar=500µm.

F Representative TRAP staining images of the femur sections from 2-wk&4-wk-old male *Osx^{Cre}; Igf2^{fl/-}* mice and littermate controls (n=5 per genotype) and statistical analysis. Scale bar=100µm.

G Representative ALP staining images of the femur sections from 2-wk&4-wk-old male *Osx^{Cre}; Igf2^{fl/-}* mice and littermate controls and statistical analysis (n=3 per genotype). Scale bar=100µm.

H Representative Immunofluorescence staining of OCN of the femur sections from 2-wk-old&4-wk-old male *Osx^{Cre}; Igf2^{fl/-}* mice and littermate controls and statistical analysis (n=3 per genotype). Scale bar=100µm.

I Representative Immunofluorescence staining of OPN of the femur sections from 2-wk-old&4-wk-old male *Osx^{Cre}; Igf2^{fl/-}* mice and littermate controls and statistical analysis (n=3 per genotype). Scale bar=100µm.

Figure S5 The expression pattern of mesenchymal markers and flow cytometry sorting before RNA-seq.

A, B The expression pattern of classic mesenchymal markers: *Cd200* and *Pdgfr*.

C Flow cytometry sorting showing the $Cd200^+$ and $CD45^-Ter119^-CD3^-$ cells were selected.

Figure S6 Biototoxicity analysis of colivelin via histopathological examinations

Representative H&E staining images of the heart, liver, spleen, lung and kidney from *Osx^{Cre}* (Ctrl) and *Osx^{Cre}; Igf2^{fl/-}* (CKO) mice with vehicle or STAT3 agonist colivelin. Scale bar=100μm.

Supplementary Table 1. Primers' sequence used for RT-qPCR

Genes		Sequence
<i>Igf2</i>	Forward	5'-GTGCTGCATCGCTGCTTAC-3'
	Reverse	5'-ACGTCCCTCTCGGACTTGG-3'
<i>Runx2</i>	Forward	5'-ATGCTTCATTGCGCTCACAAA-3'
	Reverse	5'-GCACTCACTGACTCGGTTGG-3'
<i>Alp</i>	Forward	5'-CCAACTCTTTTGTGCCAGAGA-3'
	Reverse	5'-GGCTACATTGGTGTGAGCTTTT-3'
<i>Ocn</i>	Forward	5'-AAATAGCCCTGGCAGATTCC-3'
	Reverse	5'-CAGCCTCCAGCACTGTTTAT-3'
<i>Sp7</i>	Forward	5'-ATGGCGTCCTCTCTGCTTG-3'
	Reverse	5'-TGAAAGGTCAGCGTATGGCTT-3'
<i>Colla1</i>	Forward	5'-GCTCCTCTTAGGGGCCACT-3'
	Reverse	5'-CCACGTCTCACCATTGGGG-3'
<i>Stat3</i>	Forward	5'-CAATACCATTGACCTGCCGAT-3'
	Reverse	5'-GAGCGACTCAAACAGCCCT-3'
<i>GAPDH</i>	Forward	5'-AGGTCGGTGTGAACGGATTTG-3'
	Reverse	5'-TG TAGACCATGTAGTTGAGGTCA-3'

Figure S1

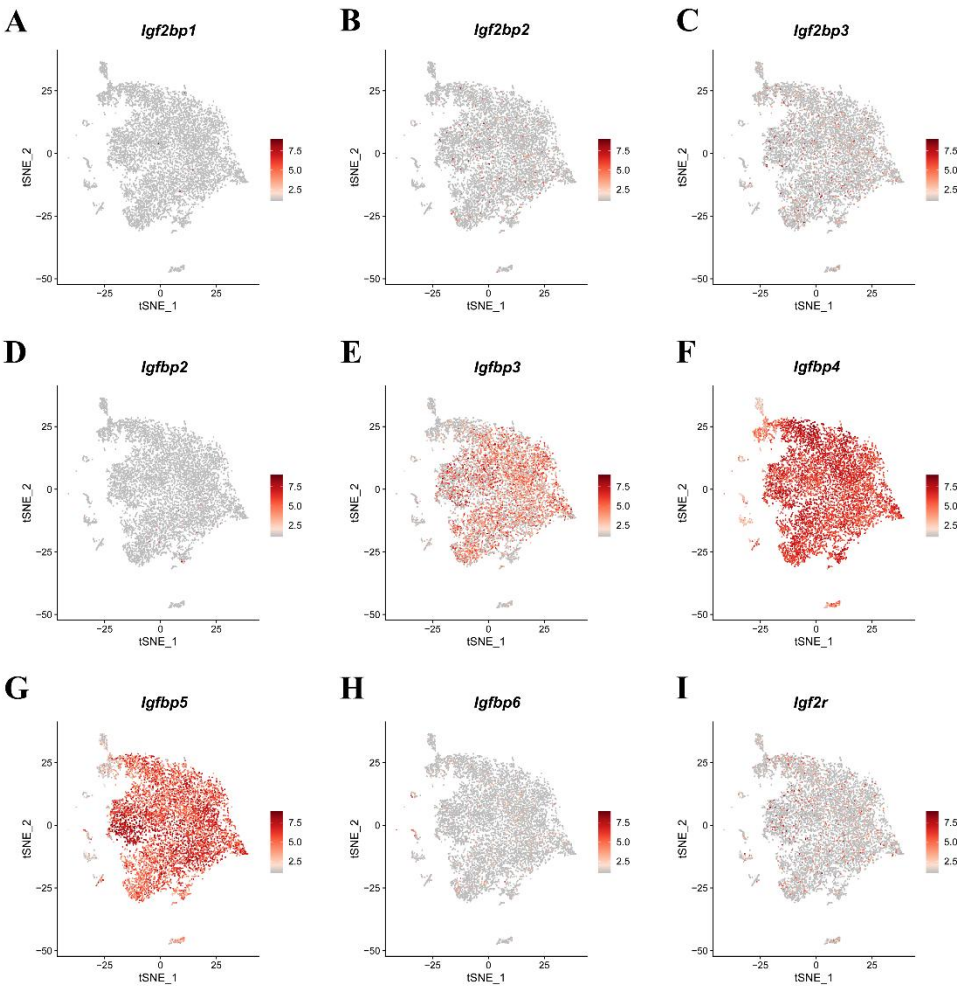


Figure S2

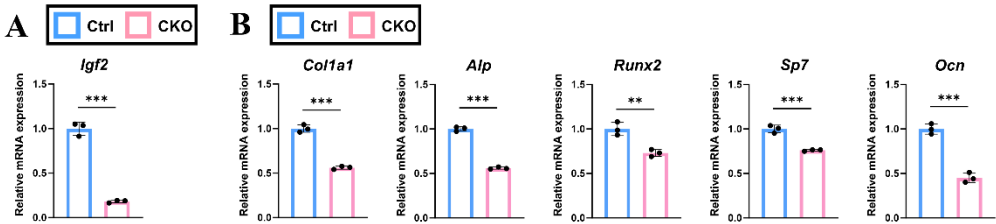


Figure S3

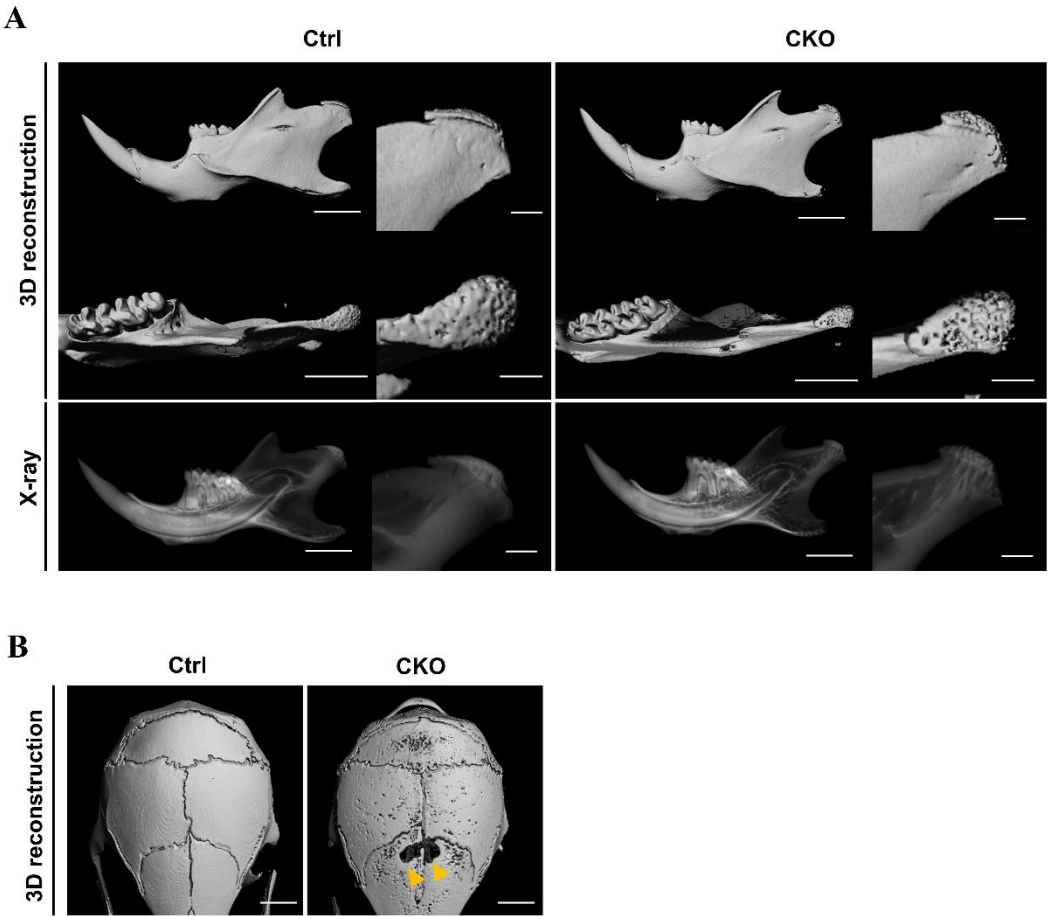


Figure S4

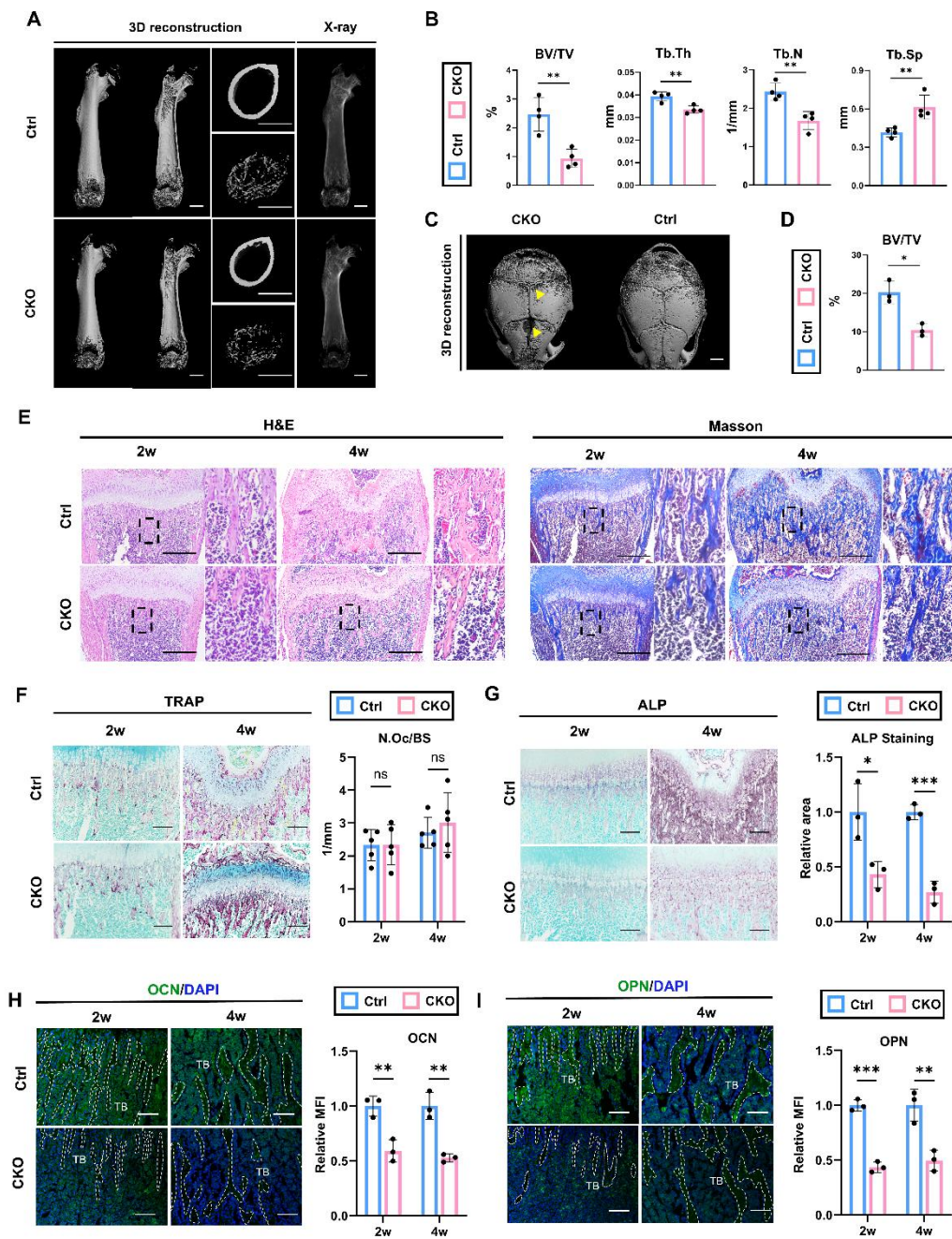


Figure S5

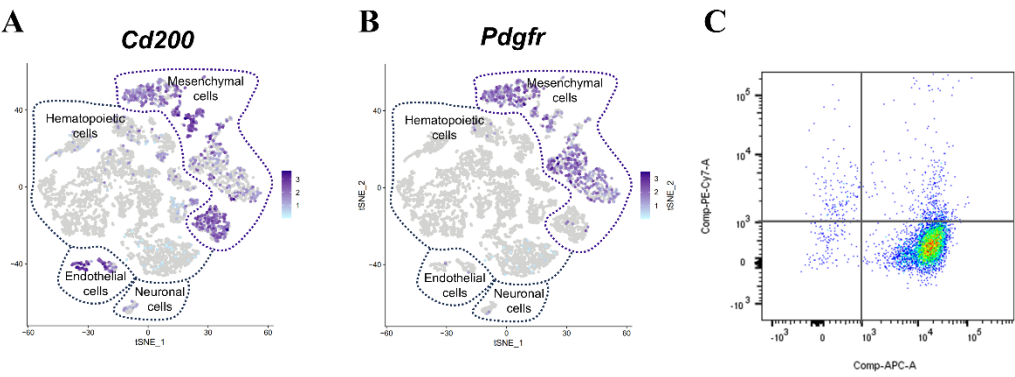


Figure S6

