Journal of Cellular Physiology

IF:3.923

Reduced PDGF-AA in subchondral bone leads to articular cartilage degeneration after strenuous running

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Date : 2019.04.17

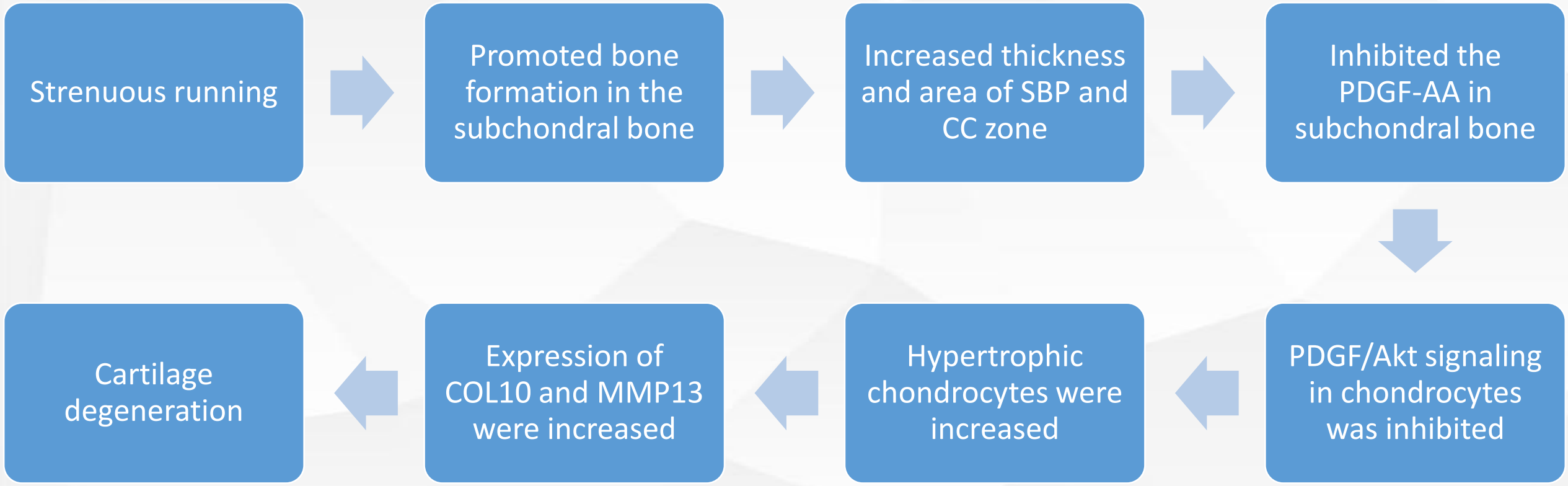
Introduction

- Platelet-derived growth factors (PDGFs), the major constituent of platelet-rich plasma and important factors in bone metabolism , were disclosed to be expressed in platelet and osteoblastic cells.

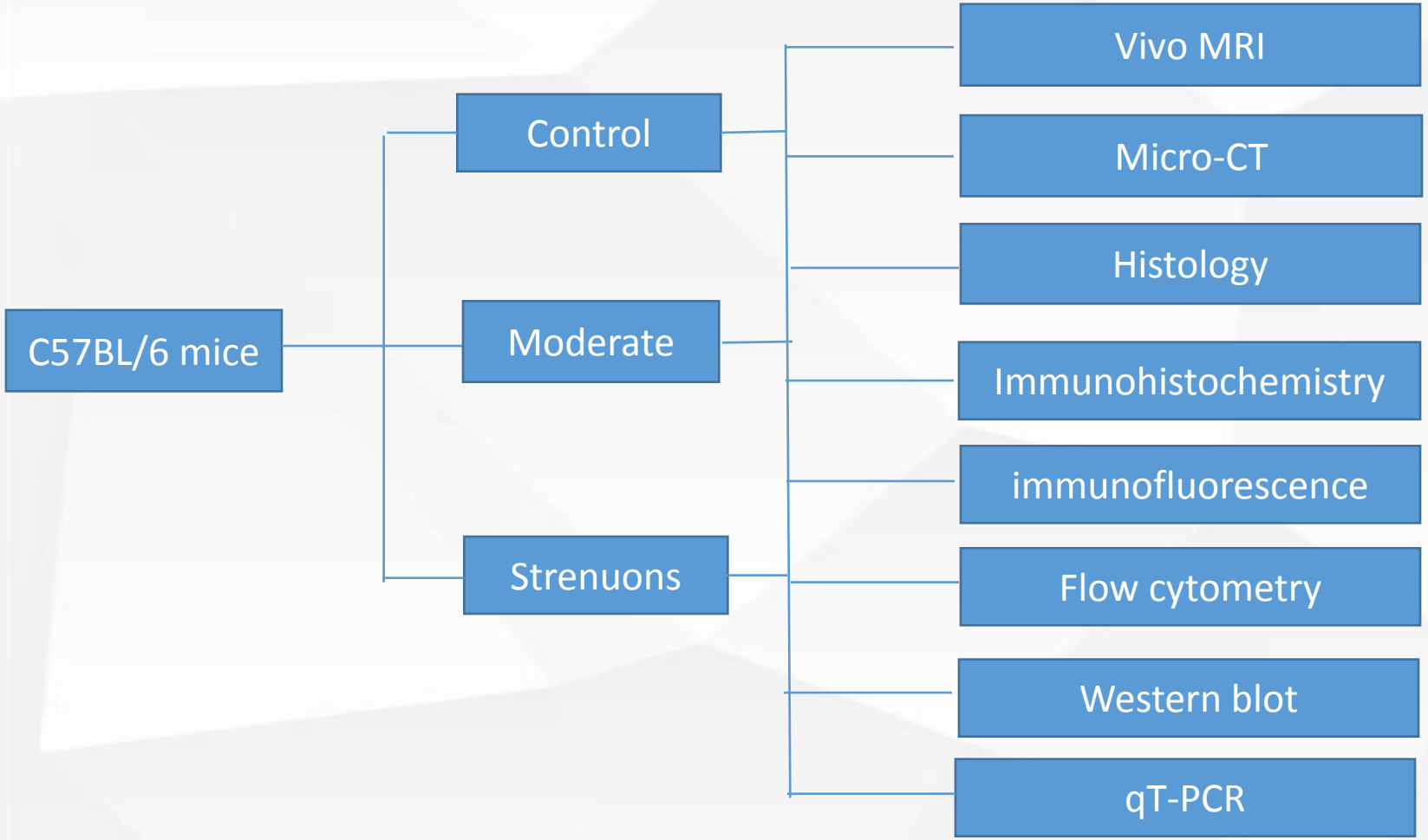
- Several studies proved that strenuous running not only induced articular cartilage erosion but also altered the balance of anabolism and catabolism in the subchondral bone of knee joint.

- It is still unknown how strenuous running affects the articular cartilage and subchondral bone, and the underlying mechanisms of cartilage degeneration remain unclear.

Hypothesis


Strenuous running
Promoted bone formation in the subchondral bone
Increased thickness and area of SBP and CC zone
Inhibited the PDGF-AA in subchondral bone
PDGF/Akt signaling in chondrocytes was inhibited
Hypertrophic chondrocytes were increased
Expression of COL10 and MMP13 were increased
Cartilage degeneration

Technology route： animals study

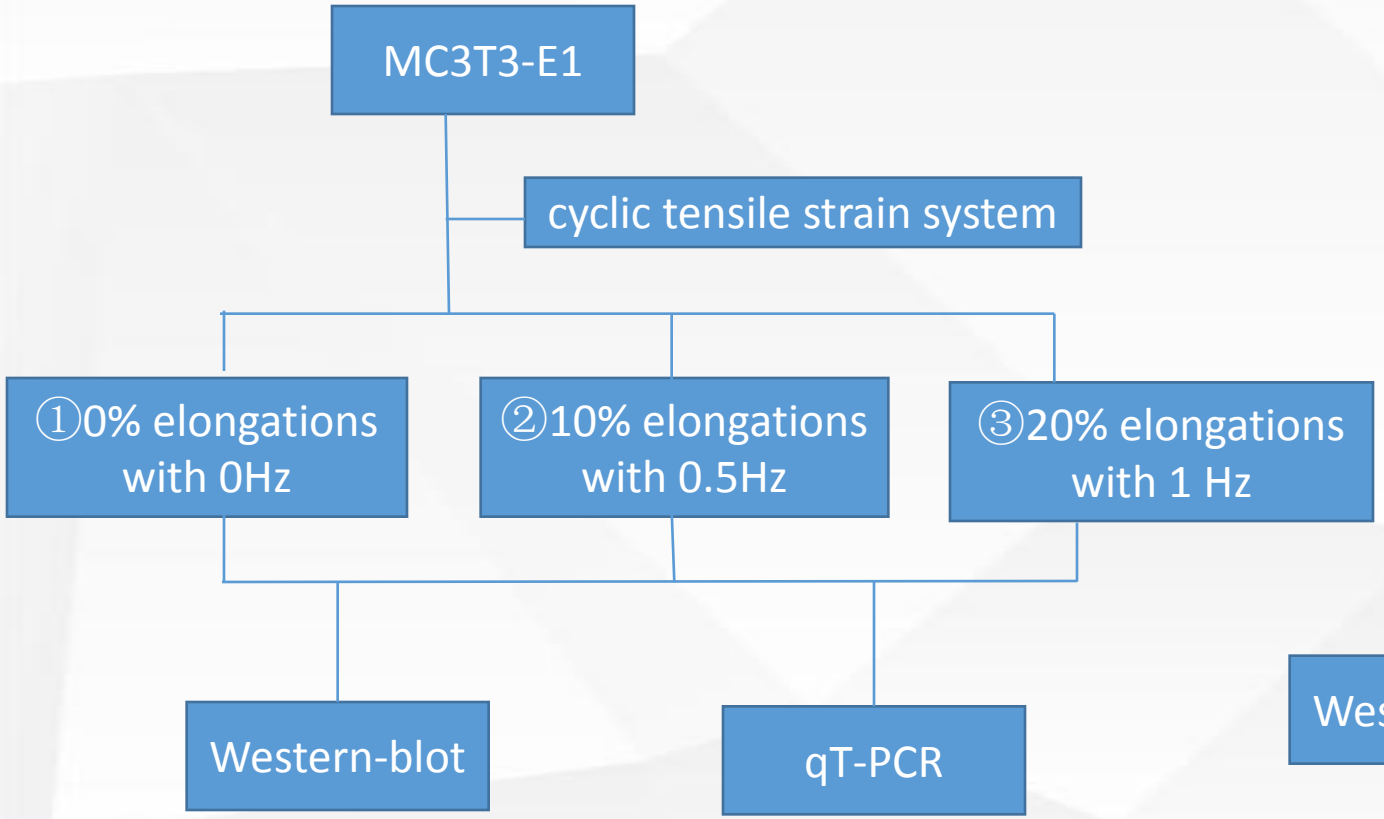


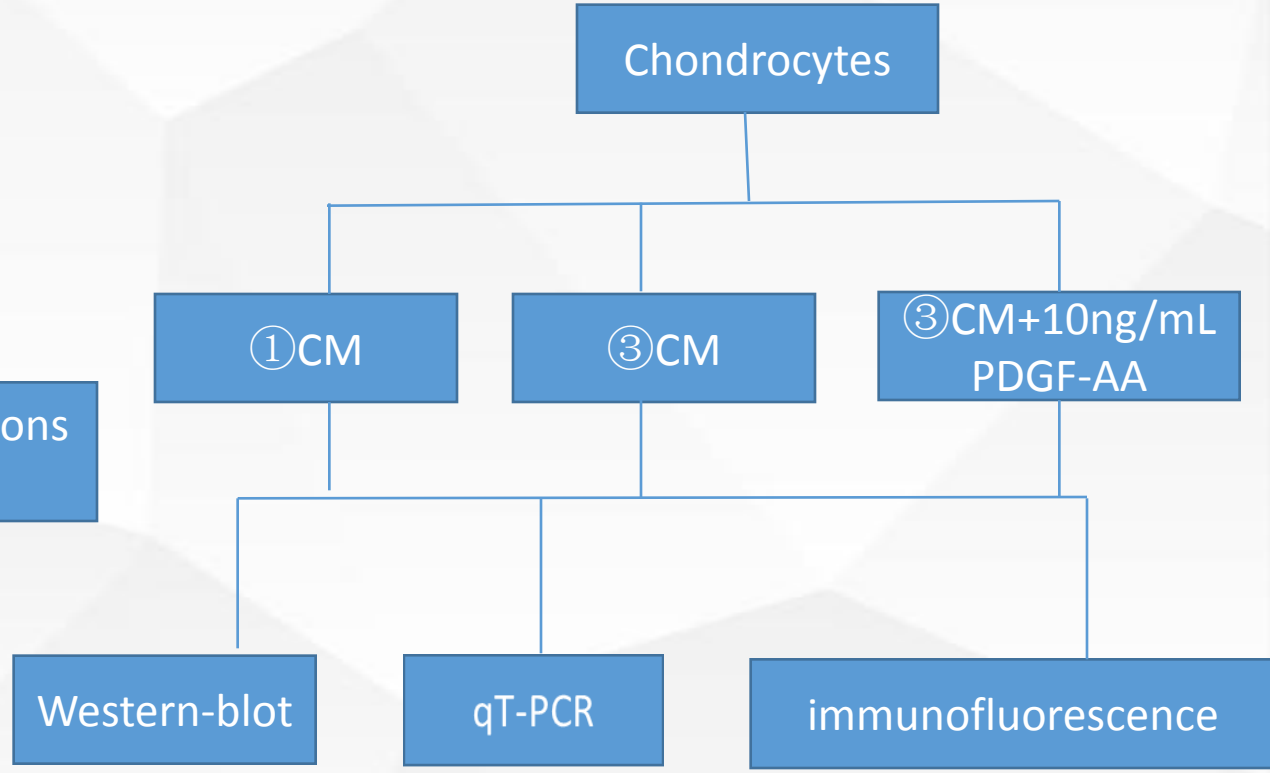
Moderate groups and Strenuons groups were subjected to treadmill running .

Moderate： In the first week , the mice started with speeds of 12 m/min The duration was 20 min per day and with the slope 0° . In the remaining 4 weeks, speeds of 18 m/min and on a 5° slope for a duration of 50min per day

Strenuons： In the first week, the mice started with speeds of 18 m/min The duration was 20 min per day and with the slope 0° . In the remaining 4 weeks, speeds of 28 m/min on a 5° slope for a duration of 50min per day

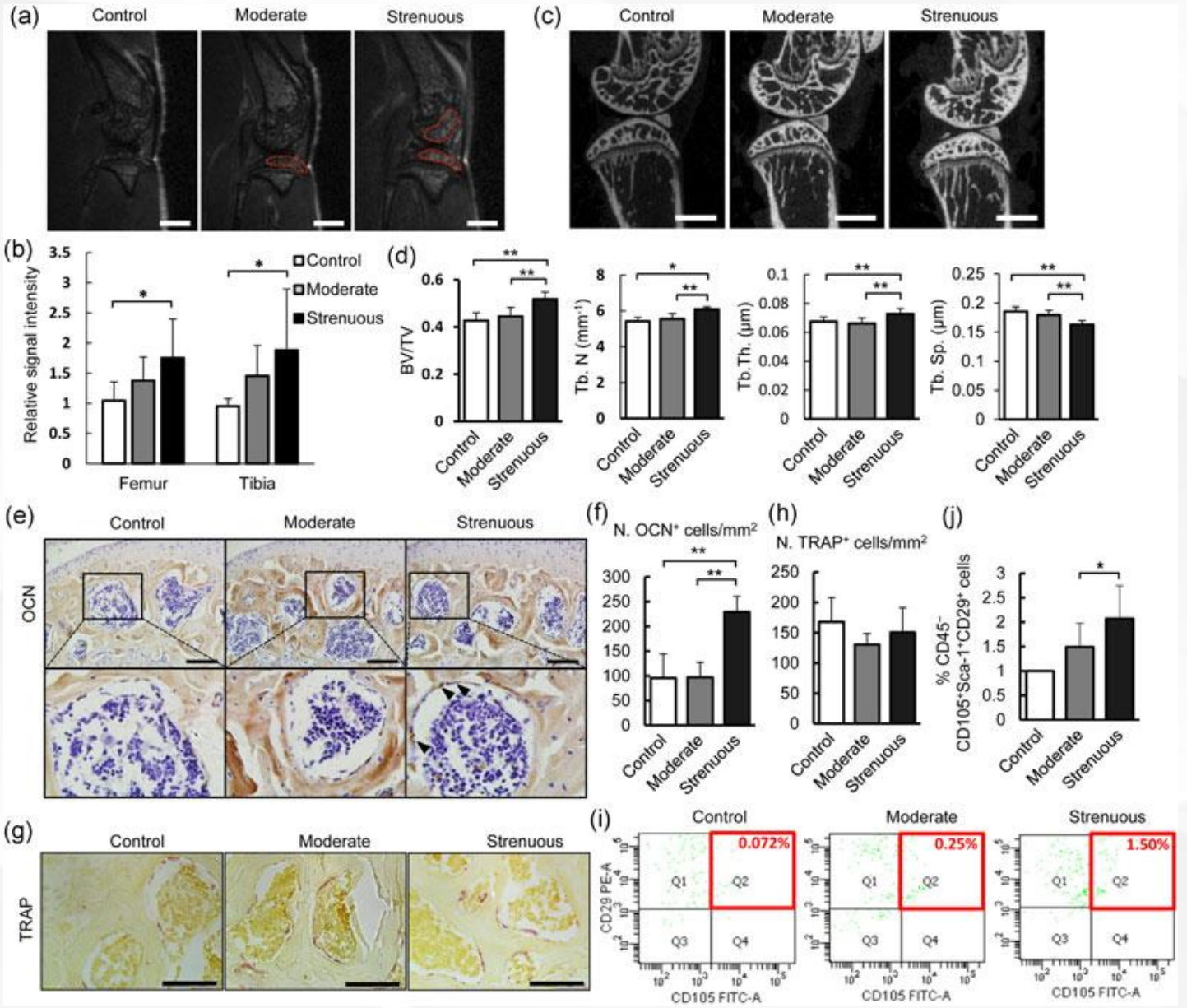
Technology route：Cell culture





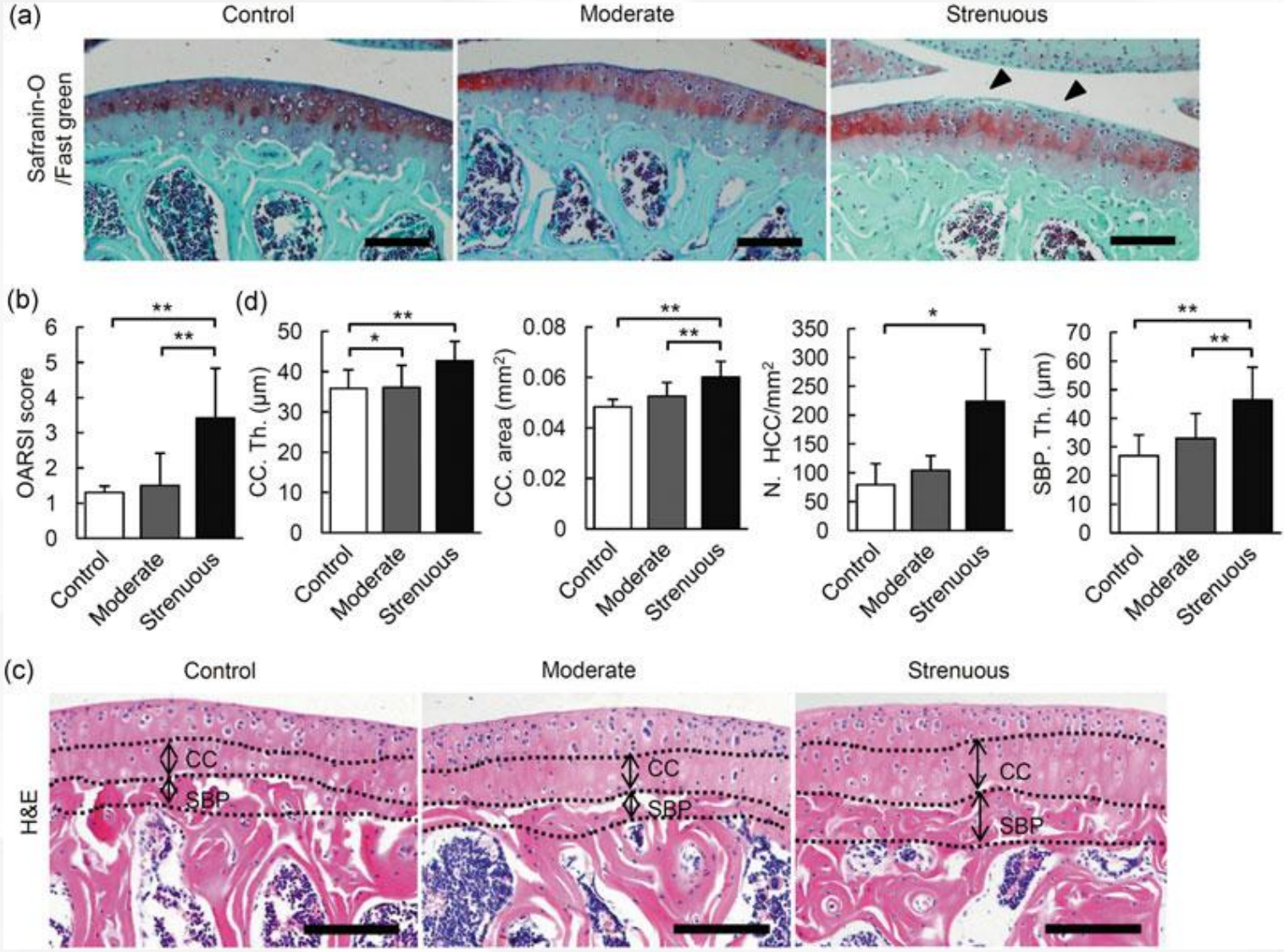
Results: Figure 1

Strenuous running induces BMLs and stimulates osteogenesis in the subchondral bone.
(a) MRI： Area with dashed lines indicates BMLs.(b) The contrast signal of bone marrow was significantly increased after strenuous running. (c) micro-CT images of sagittal sections of knee joints (d)Quantitative analysis of (BV/TV), Tb. Th, Tb. N, Tb. Sp. (e) Immumohistochemical staining of OCN in the subchondral bone. (f) Quantitative analysis of OCN+ cells. (g) Representative TRAP staining of tibial subchondral bone. (h) Quantitative analysis of TRAP+ cells. (i) Representative images of flow cytometry and (j) quantification of the percentages of CD45−, CD105+, Sca-1+, and CD29+ cells isolated from the subchondral bone marrow.



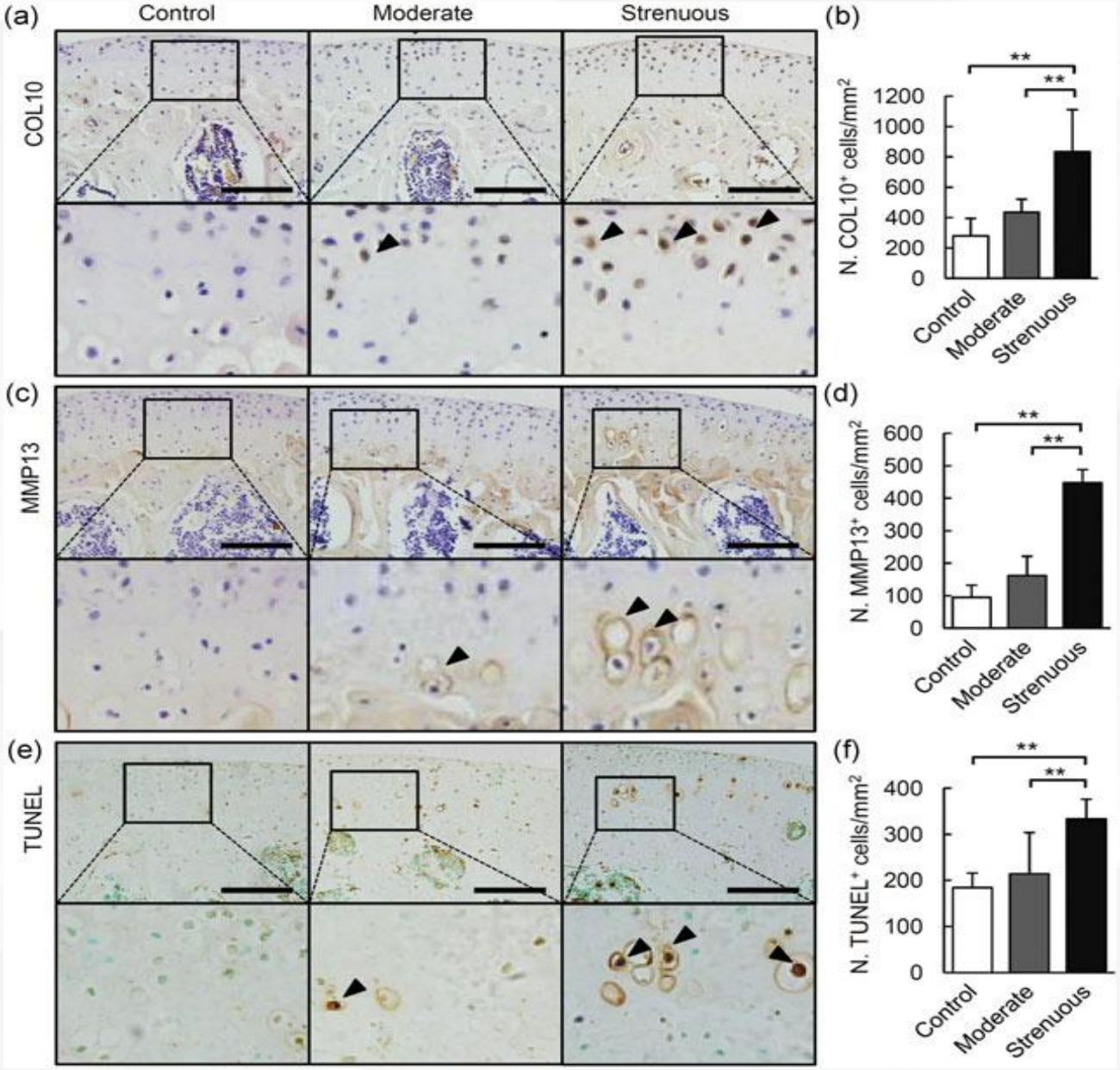
Results: Figure 2

Strenuous running alters the histomorphology of chondro-osseous junction.
(a) Safranin-O/Fast-green staining of cartilage . Black arrows point to surface discontinuity and massive proteoglycan loss in articular cartilage in the strenuous-running group. (b) OARSI scores confirm that early OA symptoms develop in tibial cartilage in strenuous-running mice. (c) H&E staining of articular cartilage in tibia plateau. (d) Quantitative analyses of thickness of calcified cartilage zone (CC. Th), area of CC zone (CC. area), number of hypertrophic chondrocytes (N. HCC) in CC zone,and thickness of subchondral bone plate (SBP. Th) in the tibial plateau



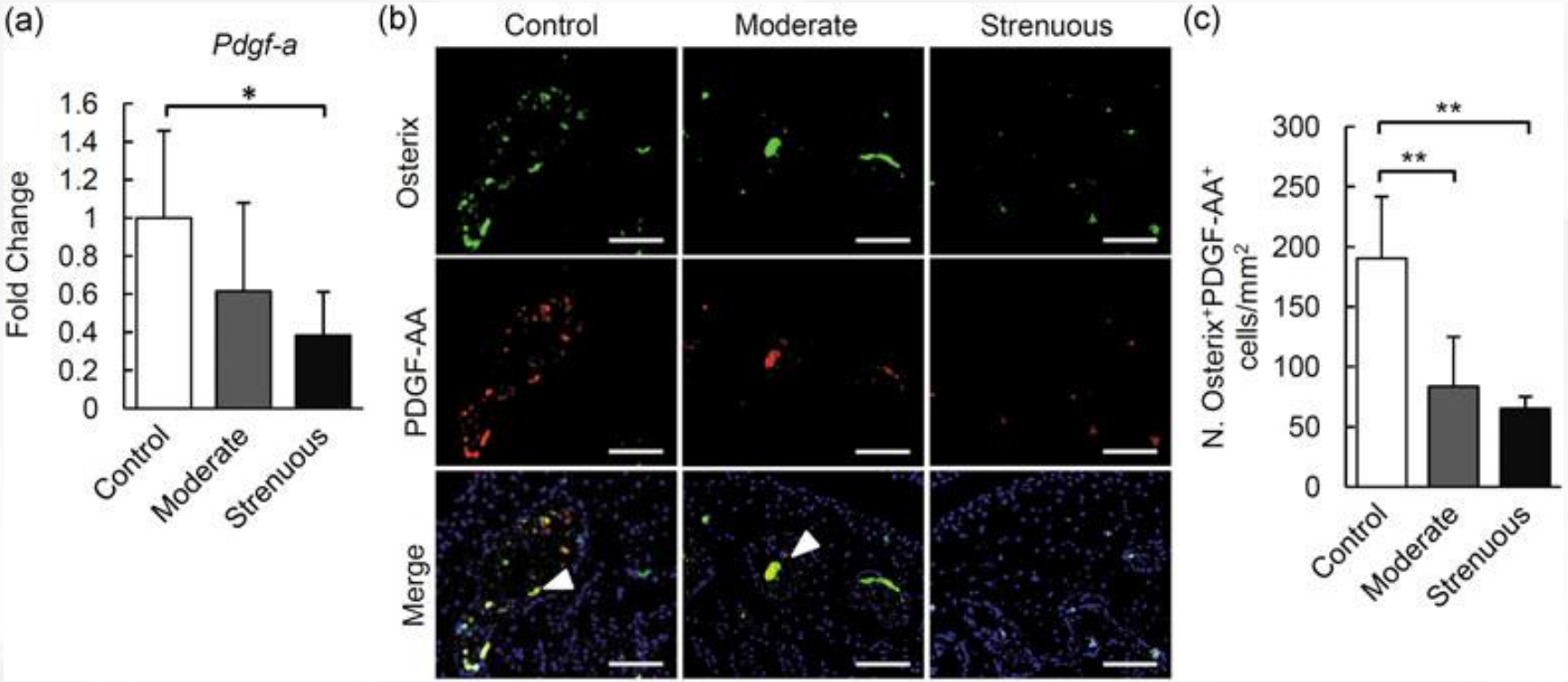
Results: Figure 3

Strenuous running promotes maturation and terminal differentiation of articular chondrocytes. Immunostaining of COL10 (a) and MMP13 (c) in articular cartilage of tibial plateau, Black arrows indicate COL10+ cells or MMP13+ cells. (b,d) Quantitative analyses of COL10+ (b) and MMP13+ (d) cells in each group. (e) TUNEL staining shows an increased number of apoptotic chondrocytes in the tibial plateau from strenuous-running group compared to the control and moderate-running groups. Black arrows point to TUNEL+ cells. (f) The number of TUNEL-positive chondrocytes per mm2 was quantified



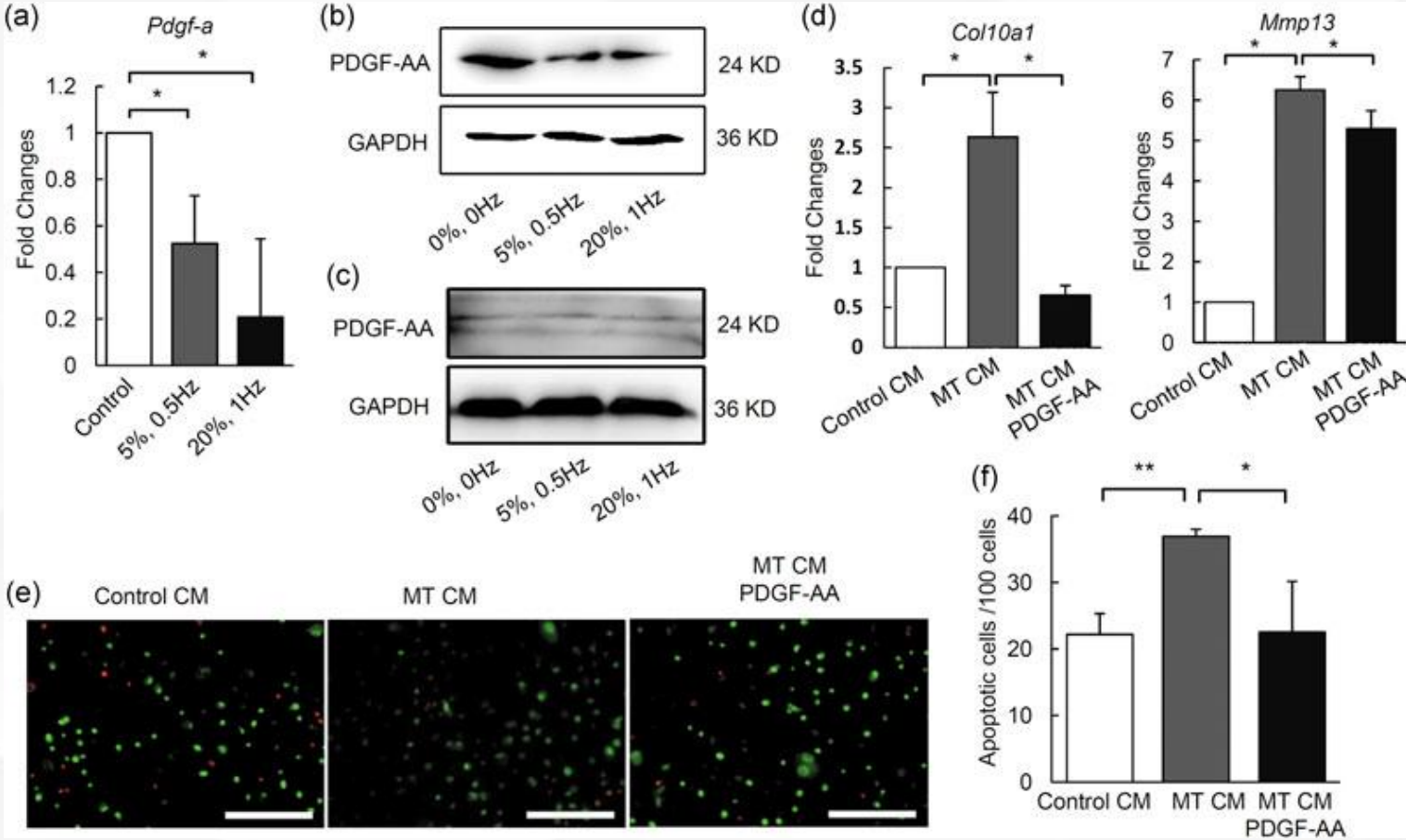
Results: Figure 4

Strenuous running suppresses the expression of PDGF-AA in osteoblastic cells of subchondral bone.
(a) qT-PCR analysis of the mRNA expression of PDGF-AA in the subchondral bone. (b) Immunofluorescence staining shows that osteoblast-lineage cells on subchondral bone surface expressed decreased PDGF-AA in strenuous-running group. (c) Quantification of the number of osterix+PDGF-AA+ cells



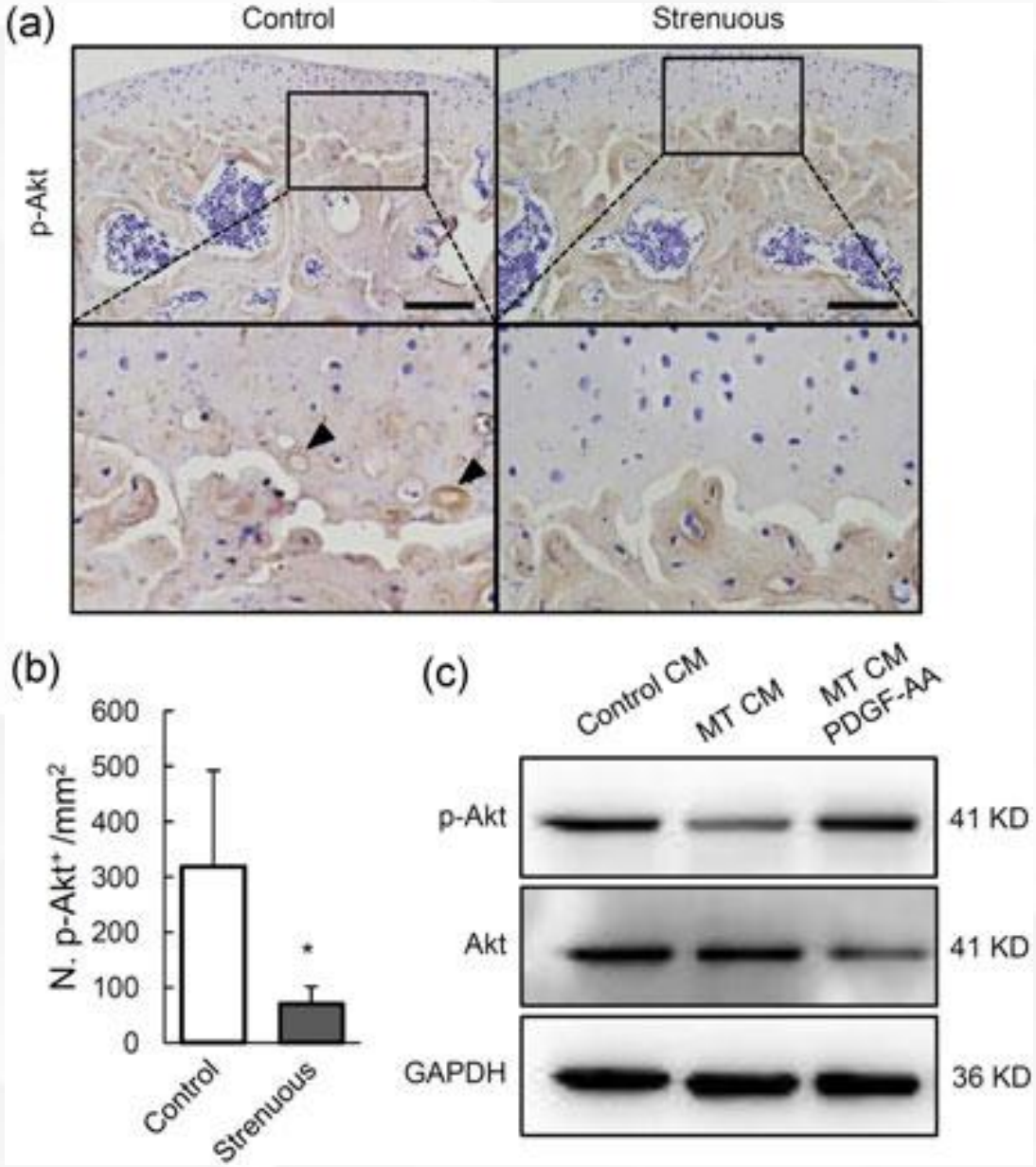
Results: Figure 5

CM from osteoblastic cells subjected to mechanical treatment stimulates terminal differentiation and apoptosis of articular cartilage.
(a,b) Preosteoblast MC3T3 was cultured in vitro and exposed to cyclic tensile strain at different intensities . Both the mRNA expression (a) and the protein levels of PDGF-AA (b) decreased in an intensity-dependent manner. (c)W-B analysis of the PDGF-AA in primary chondrocytes treated with or without mechanical loading. Expression of PDGF-AA was not altered in response to the mechanical treatments. (d) qRT-PCR analysis of the mRNA expression of Col10a1 and Mmp13 in primary chondrocytes. (e) Ethidium bromide/acridine-orange staining of primary chondrocytes. (f) Quantification of the percentages of apoptotic cells in each group



Results: Figure 6

PDGF/Akt signaling in chondrocytes is inhibited by reduced transport of PDGF-AA.
(a) Immunostaining of phosphorylated Akt (p-Akt) in articular cartilage. Black arrows indicate p-Akt+ cells.(b) Quantification of p-Akt+ cells in the calcified zone of cartilage. The number of p-Akt+ chondrocytes was reduced significantly in the strenuous-running group compared with the control group . (c) The p-Akt was downregulated in primary chondrocytes cultured with the mechanical treatment condition medium (MT CM), but PDGF-AA treatment rescued the inhibitory effect of MT CM on p-Akt expression;



Discussion

- This study demonstrated that the PDGF-AA from subchondral bone might regulate differentiation of chondrocytes in articular cartilage.

- This study showed that strenuous running-induced proteoglycan loss,elevated the expression of MMP13 and COL10, and stimulated apoptosis in the chondrocytes of articular cartilage.

- This study found that PDGF-AA, synthesized and secreted from the osteoblasts in subchondral bone, was downregulated, and that the PDGF/Akt signaling of chondrocytes was suppressed, which might be a crucial cause for cartilage degeneration after strenuous running.

Conclusions

- The study demonstrates that running at a high speed or intensity,rather than a long-distance running, may cause cartilage degeneration.
- The study has found that transport of PDGF-AA from subchondral bone to articular cartilage plays an important role in cartilage degeneration during strenuous running.
- Strenuous running suppresses synthesis of PDGF-AA in subchondral bone and, consequently, the activity of PDGF/Akt signal pathway in articular cartilage is downregulated,which may be associated with cartilage degeneration

THANK YOU