Biomedicine & Pharmacotherapy 114 (2019) 108811

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy IF：3.742

journal homepage: www.elsevier.com/locate/biopha

(二十二碳六烯酸，DHA)

Docosahexaenoic acid inhibits bone remodeling and vessel formation in the osteochondral unit in a rat model

Yinhao Xie, Wei Zhou, Zhihong Zhong, Haotao Yu, Ping Zhang*, Huawei Shen

Department of Orthopaedics, The Third Affiliated Hospital of Guangzhou Medical University, No. 63, Duobao Road, Liwan District, Guangzhou, Guangdong Province, China

汇报人：赵鑫

2019.08.14

Contents

Introduction

- All of the components of the joint are affected in OA disease, while the osteochondral unit is still a critical part of progression of OA.
- It plays an important role in load transfer during weight-bearing and joint motion and changes along with the evolution of OA.

Introduction

◆In early-stage OA, the speed of bone remodeling of the cortical plate and subchondral bone is increased, accompanied by decreased bone mass and increased porosity.

◆These changes in the osteochondral unit may cause degradation of cartilage because of abnormal mechanical loading and outside intervention.

◆Therefore, the osteochondral unit is a reasonable and effective target for treatment of OA.

Introduction

- Docosahexaenoic acid (DHA) is pervasive and easily accessible which directly from fish oil, maternal milk, or algae. DHA supplements are popular in daily life.
- A cross-sectional study showed that intake of n-3 polyunsaturated fatty acids had a positive correlation with bone mineral density in postmenopausal women.

Introduction

In this study, The author aimed to determine whether DHA has the ability to maintain integrity of the osteochondral unit and cartilage function.

Materials and Methods

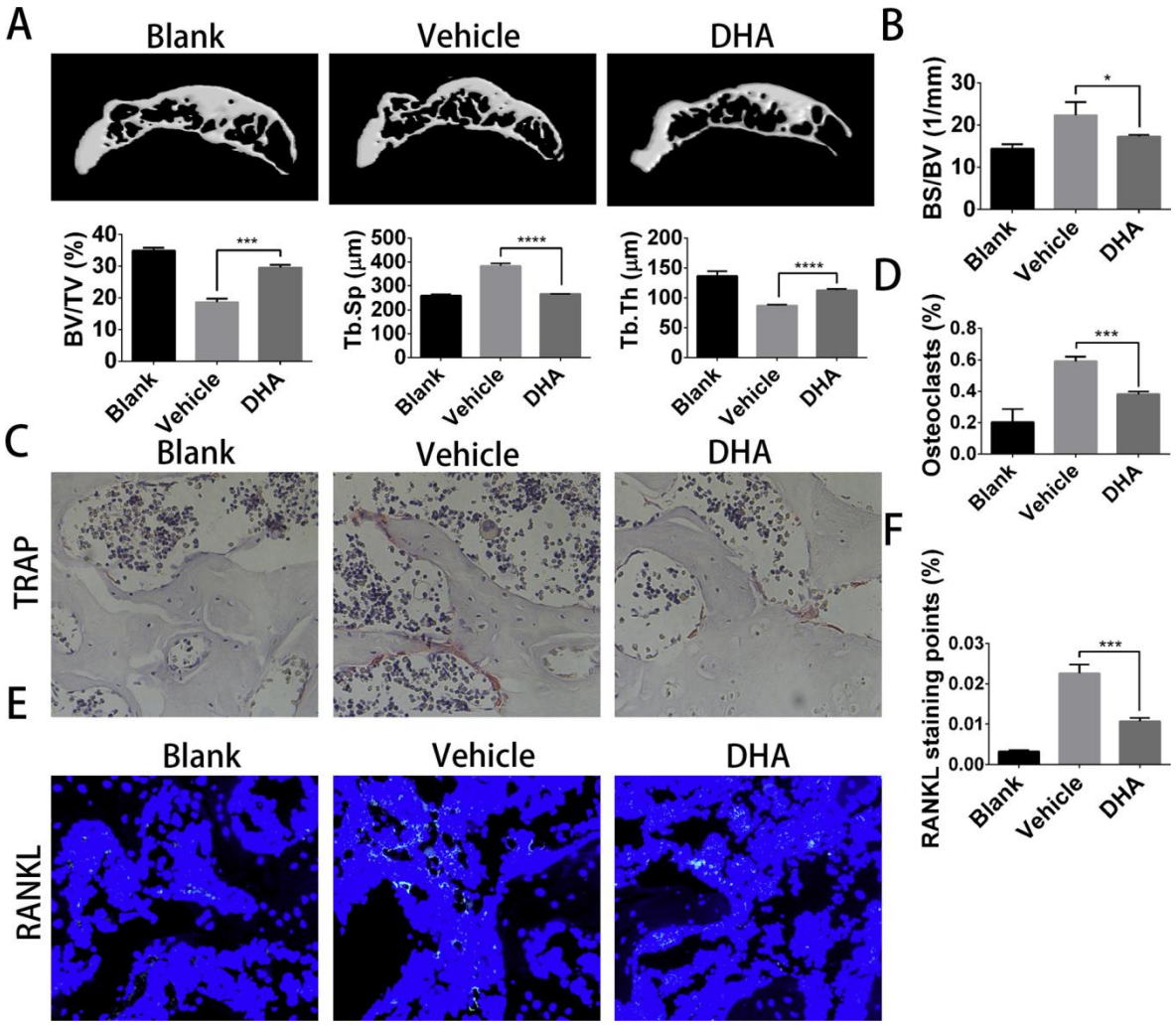
- Twelve-week-old male SD rats
  - Group 1 Sham group,
  - Group2 The vehicle-treated ACLT group,

Group 3 ACLT-operated and treated with DHA group (1 mg/kg

concentration in tail vein every other day for two months).

- RAW264.7 cells were used estimate the effects of DHA on osteoclast differentiation.
- Human umbilical vein endothelial cells (HUVECs) were

Results

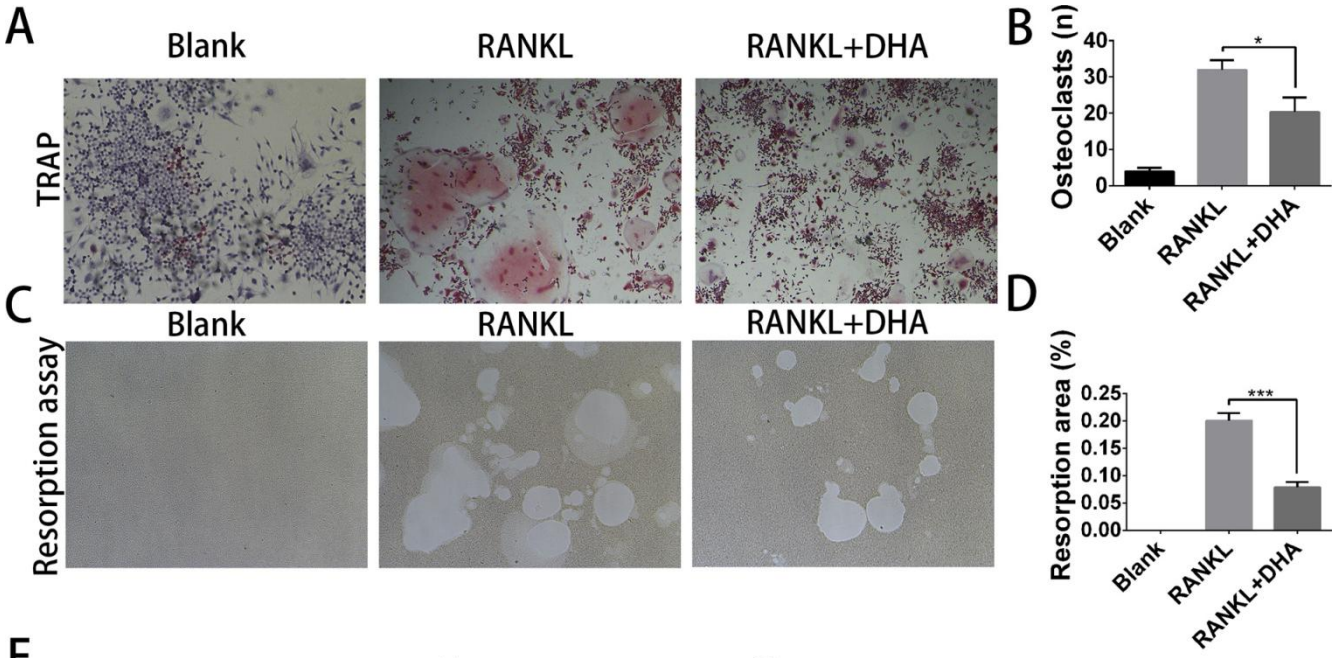


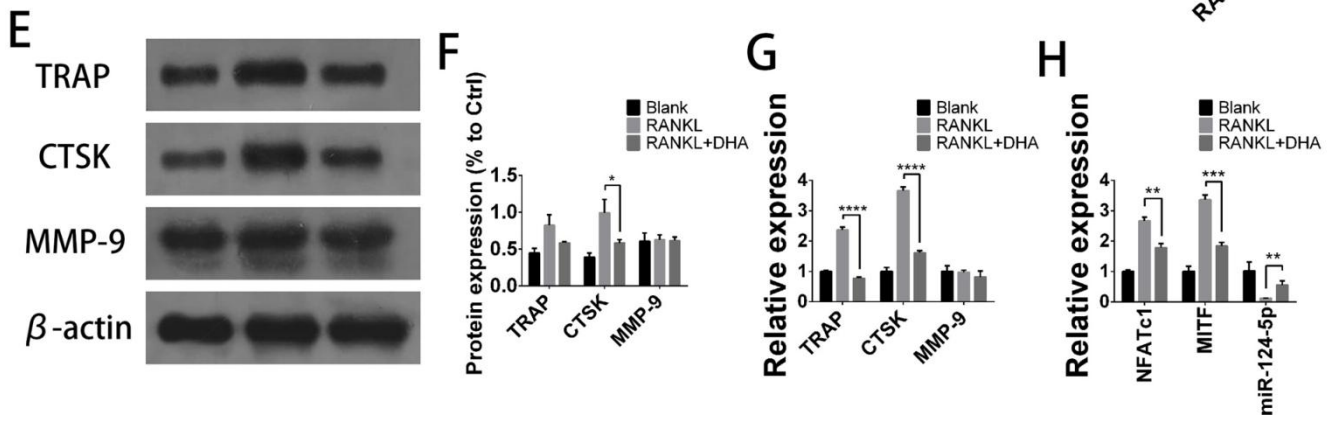
✓**micro-CT**：DHA group led to a higher ratio of bone volume to tissue volume and trabecular thickness；the ratio of the bone surface to bone volume and trabecular separation were lower.

✓**TRAP staining** show percentage of osteoclast cells were higher in the vehicle-treated group.

✓**RANKL expression** was significantly higher in the vehicle-treated group.

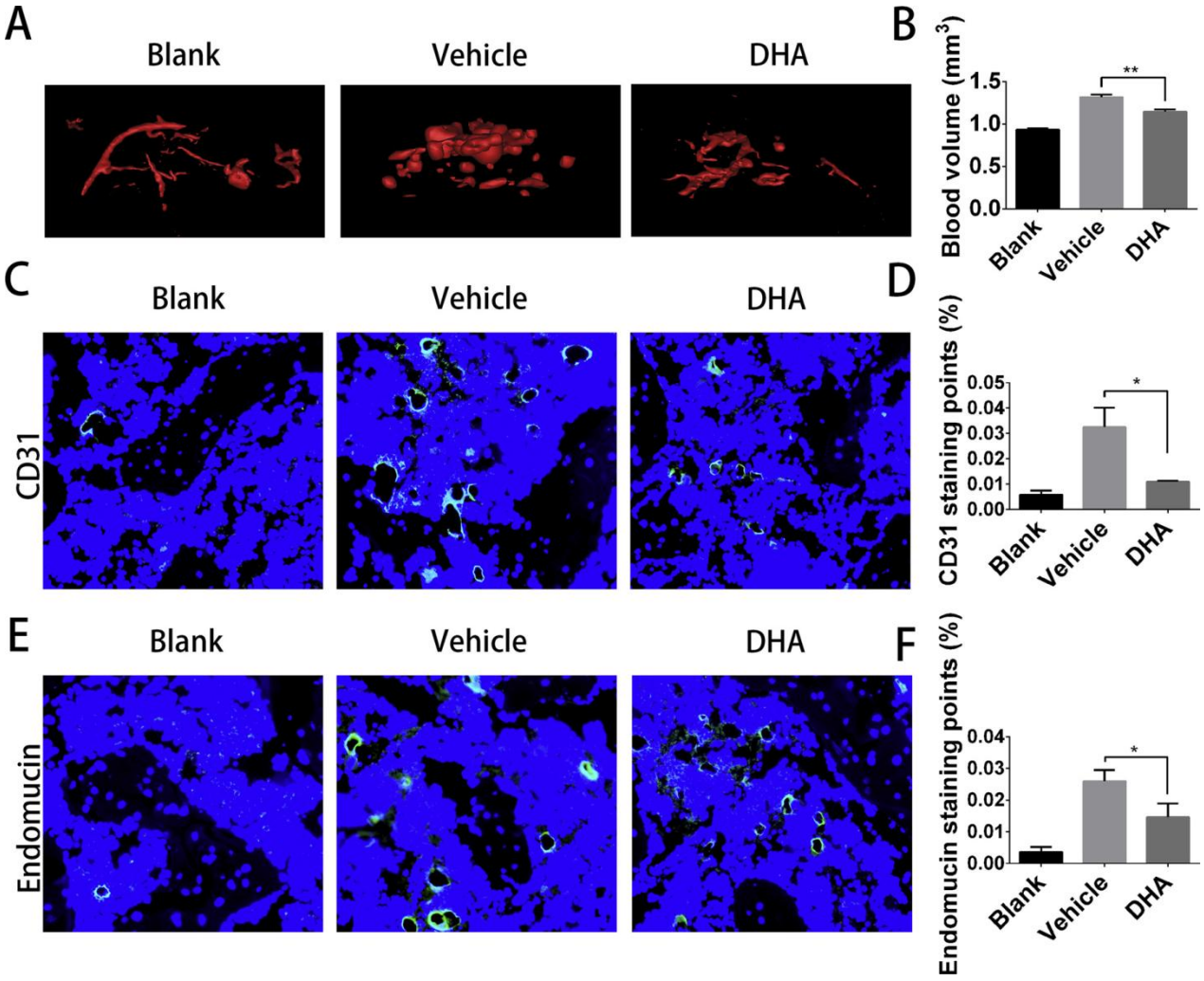
Results





- **RAW264.7:**The numbers of TRAP-positive cells were significantly lower in the DHA-treated group.
- **Corning osteo-assay plates:**DHA-treated RAW264.7 cells showed a lower area of resorption pits.
- **real-time PCR and western blot:**CTSK mRNA and protein and TRAP protein expression was suppressed.

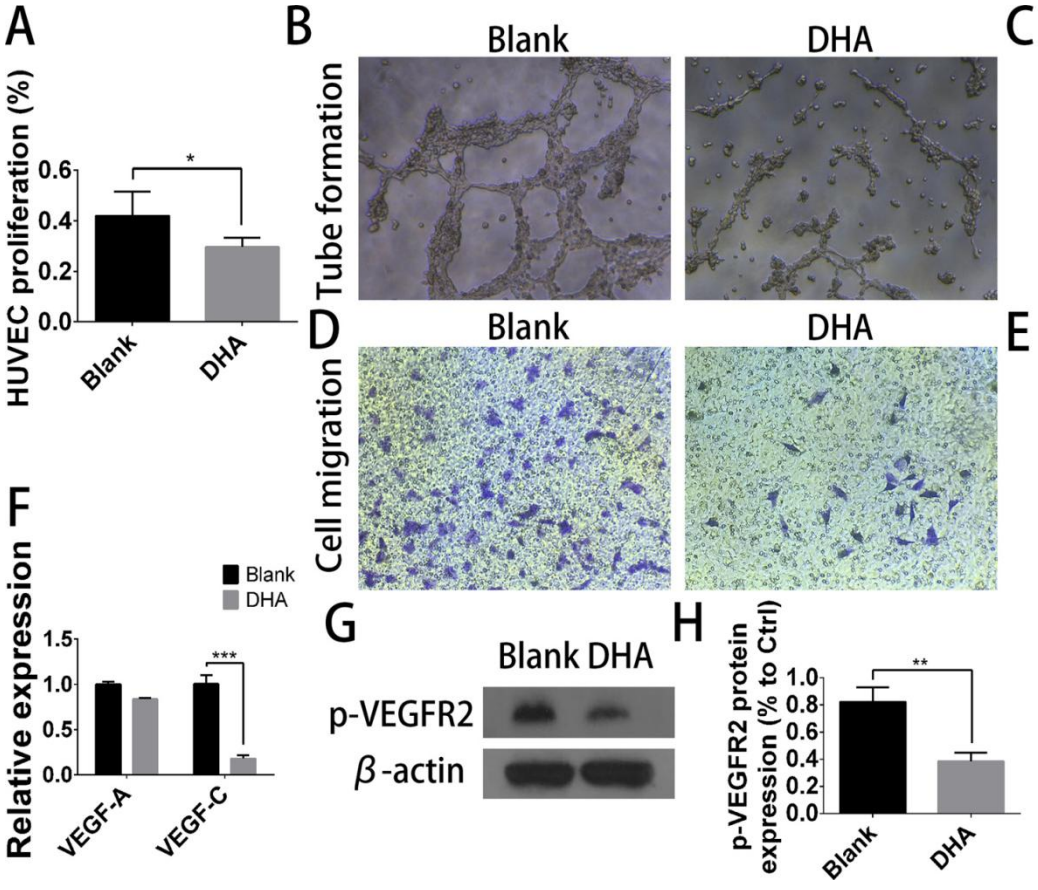
Results



◆**micro-CT-based angiography:**The volume of blood vessels was significantly higher in the vehicle-treated group.

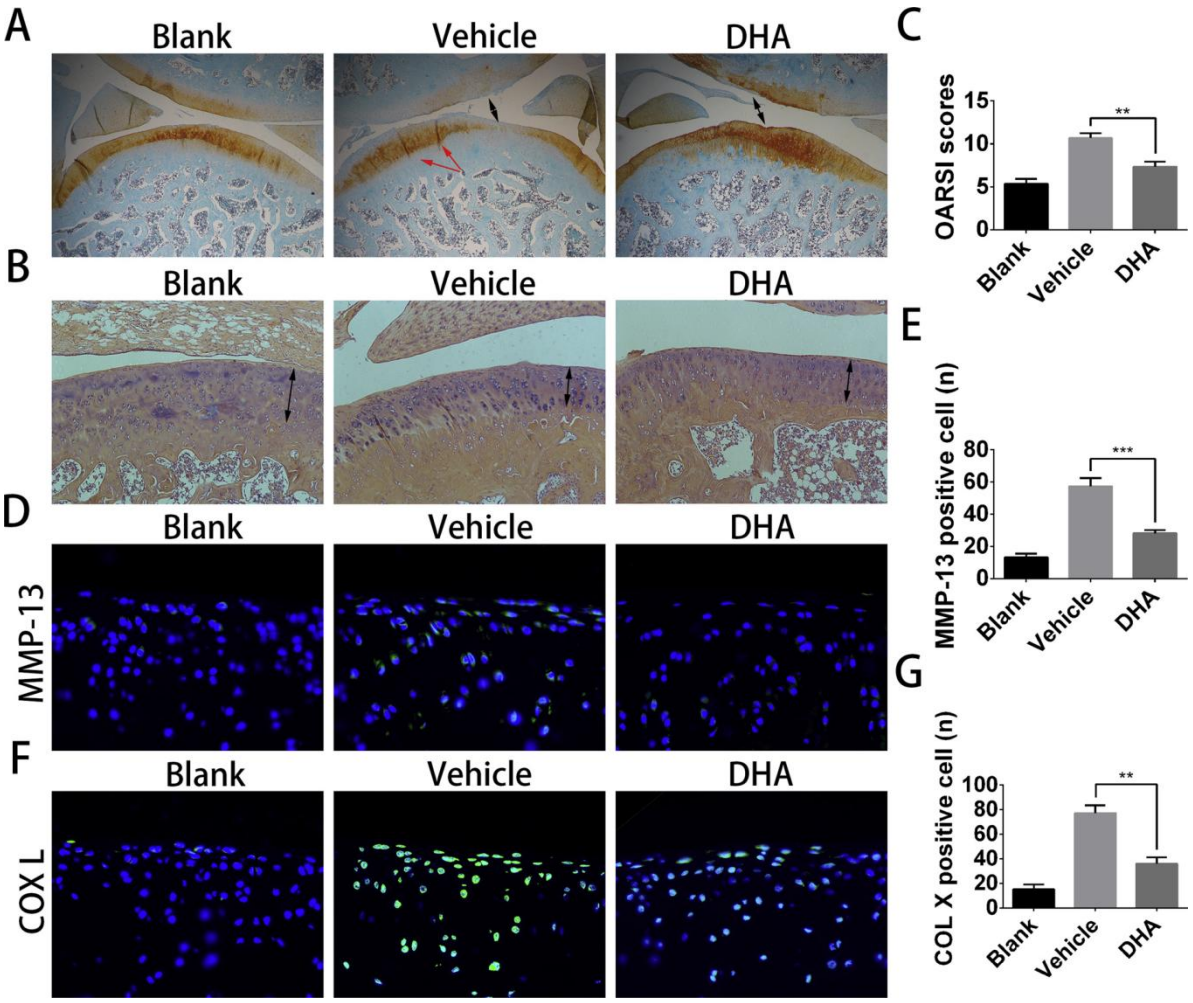
◆**Immunofluorescence Staining:**CD31 and endomucin staining was significantly stronger in the vehicle-treated group.

Results



DHA-treated HUVECs : The endothelial tube formation and HUVEC migration of extracellular proteins was inhibited. VEGF-C and VEGF-A mRNA levels and VEGFR2 were remarkably lower in DHA-treated HUVECs.

Results



- **Safranin O staining** showed that proteoglycan wasreduced.
- **HE** showed that the thickness of the calcified cartilage zone was lower.
- **MMP-13 and collagen X** levels in articular cartilage were reduced.

Discussion

- In this study, we found that DHA had the capacity to reduce the remodeling speed of subchondral bone and inhibit vessel formation.
- In healthy circumstances, the balance of osteoclasts and osteoblasts is regulated to adapt to mechanical loading of bone structure by carrying out bone resorption and formation. Bone remodeling underneath cartilage is detrimental when the balance is broken.
- TRAP, CTSK, and MMP-9 are regarded as markers of osteoclasts because of their high expression in cells. DHA reduces osteoclast formation by inhibiting specific gene expression of osteoclasts, which further affects bone resorption.

Discussion

- Increased bone remodeling and plentiful blood vessels in subchondral bone are necessary steps for development of OA.
- DHA may ameliorate progression of OA via repressing angiogenesis in the interface between subchondral bone and calcified cartilage.
- proliferation and migration of HUVECs were significantly suppressed in the DHA-treated group compared with the vehicle-treated group.
- DHA inhibited blood vessel formation by blocking the VEGF–VEGFR2 signaling pathway, which improved cartilage degeneration.

Conclusion

In conclusion, supplementation with DHA protects against cartilage degeneration in ACLT-operated rats. Our study supports the notion that subchondral bone may be a therapeutic target for OA.