FACULTY OF MEDICINE AND HEALTH SCIENCES

Beyond inflammation: GDF15's influence on bone remodeling in arthritis

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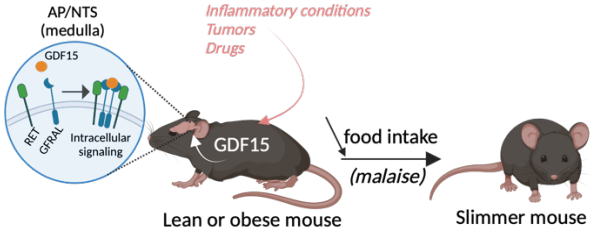
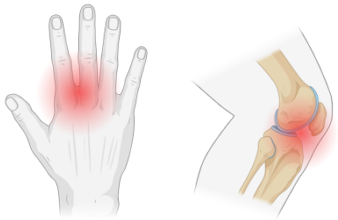
GHENT UNIVERSITY

VIB science meets life

BACKGROUND

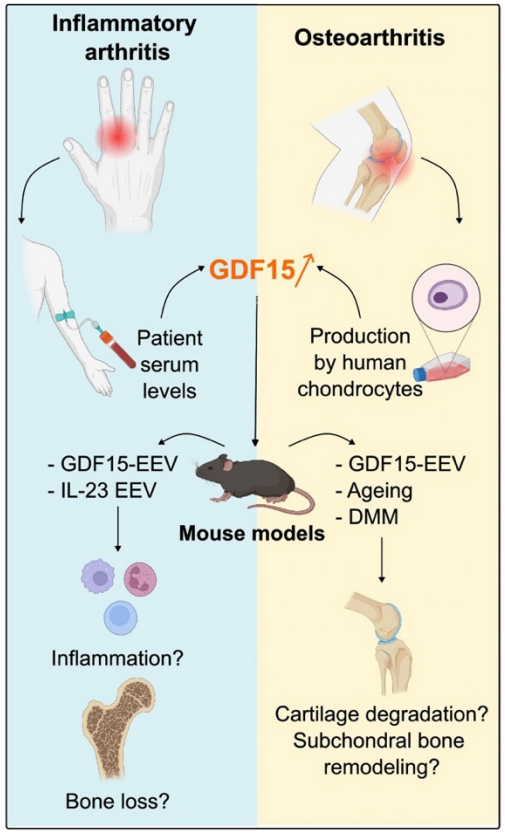


- GDF15 (Growth Differentiation Factor 15) is a metabolic factor able to induce weight loss
- It reduces food intake by binding to its receptor GFRAL in the hindbrain
- Serum GDF15 is elevated in many inflammatory conditions, but whether it acts pro-/anti-inflammatory is contested



- Rheumatoid arthritis (RA), Psoriatic Arthritis (PsA) and Osteoarthritis (OA) are musculoskeletal diseases associated with joint pain and stiffness
- RA and PsA are **immune-mediated inflammatory diseases**, affecting more than just the joint
- OA is a **local joint disease**, hallmarked by cartilage degradation but affecting the whole joint
- RA, PsA and OA are associated with metabolic conditions such as obesity
- RA, PsA and OA are associated with local or systemic bone adaptations

AIM



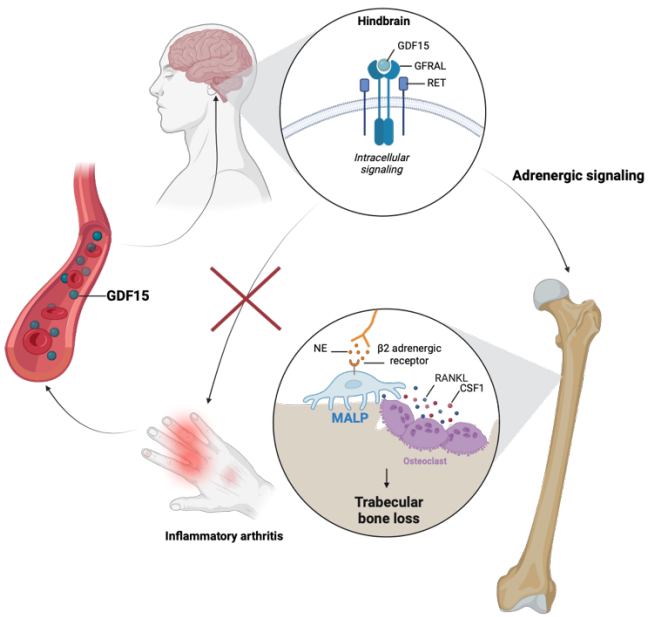
→ Is GDF15 involved in the pathogenesis of inflammatory arthritis and OA?

→ Use of mouse models to potentially advance understanding of disease mechanisms

→ Additional focus on bone remodeling

Research paper 1

GDF15 mediates inflammation-associated bone loss through a brain-bone axis



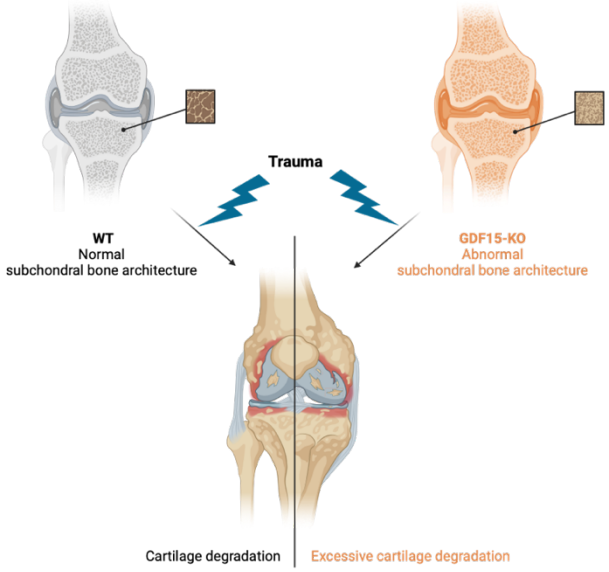
Key findings:

- GDF15 is a novel bone loss inducer, but not a pro-inflammatory mediator
- In inflammatory conditions, GDF15 mediates bone loss independent of inflammation severity

  → Explanation why patients can still suffer from bone loss, while inflammatory symptoms are under control
- Bone loss is induced through a brain-bone axis
- The brain sends adrenergic signals to MALP cells in the bone, which will stimulate osteoclasts (specialized cells) to resorb bone
- Potential to manipulate this axis through beta blockers

Research paper 2

An altered subchondral bone architecture increases the risk of cartilage degradation after trauma



Key findings:

- Chondrocytes derived from OA-patients express more GDF15 protein than healthy controls
- In a traumatic injury model for OA, GDF15 deficient mice suffer from more severe cartilage degradation
- This is not true in aging-induced OA
- GDF15 deficient mice show an abnormal subchondral bone architecture
- The subchondral bone is equally affected after trauma in GDF15 deficient mice as in control mice
- We speculate that the abnormal architecture causes excessive OA development after traumatic injury

Thesis submitted to fulfill the requirements for the degree
"Doctor of Health Sciences"

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