Center of Experimental Rheumatology

Modic type 2 changes are fibroinflammatory changes with complement system involvement adjacent to degenerated vertebral endplates

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Introduction

Modic type 2 changes (MC2)

- Painful vertebral endplate signal intensity changes visualized by magnetic resonance imaging (MRI)
- Associate with intervertebral disc (IVD) degeneration and vertebral endplate damage
- Hallmarks: Inflammation, fibrosis, fatty marrow
- **Inflammatory MC2 pathomechanisms** and **their association with endplate degeneration is unknown**

Aims

1. **To investigate the degree of bony (BEP) and cartilage endplate (CEP) degeneration in MC2**
2. **To identify inflammatory MC2 pathomechanisms**
3. **To identify MC2 bone marrow changes that correlate with severity of endplate degeneration**

Methods

- Two human lumbar (L1-S1) cadaveric spines with MC2 and control vertebrae were used
- For every region of interest, pairs of axial biopsies (n=58) spanning the entire vertebral body including both CEPs were collected (**Figure 1**)
- **Biopsy 1A**: Processed for paraffin histology. BEP / CEP degeneration was scored according to the standardized endplate degeneration scoring system for human IVD degeneration[1]
- **Biopsy 1B**: Endplate-near bone marrow was analyzed with mass spectrometry. Differentially expressed proteins (DEPs) between MC2 and control; bioinformatic overrepresentation analysis (ORA) was performed.
- Endplate scores were correlated with DEPs.

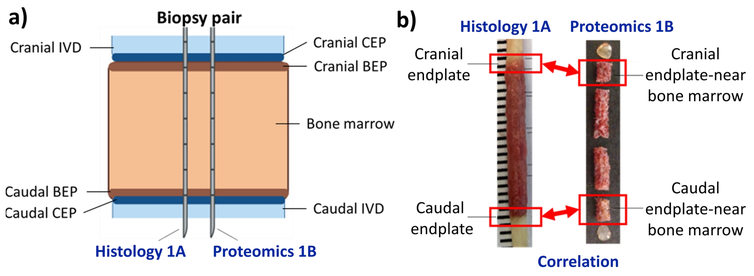
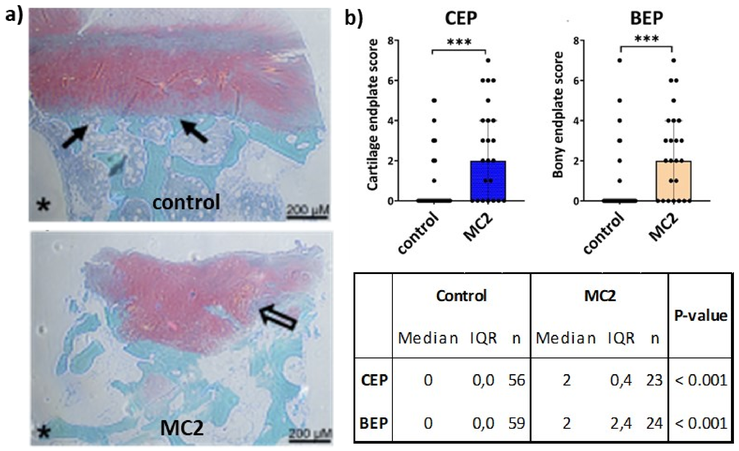


Figure 1. a) Illustration of biopsy pair collection and b) representative image of collected biopsies subjected to histological and proteomic analysis.

Results

1. MC2 occur adjacent to more degenerated vertebral endplates with lost CEP/BEP boundaries

- 79 CEPs and 83 BEPs were evaluated (**Figure 2**)
- **CEP / BEP degeneration** scores: Significantly **increased in MC2**
- **CEP/BEP boundaries: Often completely lost in MC2**



	Control			MC2			P-value
	Median	IQR	n	Median	IQR	n	
CEP	0	0,0	56	2	0,4	23	< 0.001
BEP	0	0,0	59	2	2,4	24	< 0.001

*Figure 2. a) Representative histology pictures (4x) of control (top) and MC2 (bottom) bone-disc junctions. Filled arrows: Intact bone-disc junction; clear CEP/BEP boundaries. Open arrows: Endplate damage with disrupted CEP/BEP boundaries in MC2; *bone marrow site. b) Distribution endplate degeneration scores (top) and statistics (bottom).*

2. MC2 endplate-near bone marrow contains more complement system components, extracellular matrix (ECM) proteins and angiogenic factors

- Detected proteins: **2534**; differentially expressed proteins (DEPs) MC2 vs control: **318** (control: n=69, MC2: n=30)
- Increased **complement system-**, **ECM (fibrosis)**, **angiogenic**, and **neurogenic proteins in MC2 endplate-near marrow** (**Figure 3**)

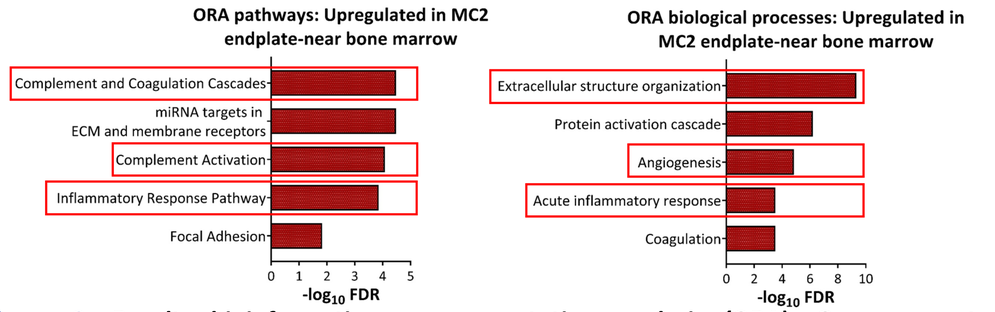


Figure 3. Results bioinformatic overrepresentation analysis (ORA). Overrepresented pathways (left) and biological processes (right) in MC2 vs. control endplate-near bone marrow protein composition.

3. Complement- and neurogenic proteins correlate with endplate degeneration

- 318 DEPs between MC2 and control were correlated with histological BEP and CEP scores
- ORA of **DEPs with correlation** coefficient ρ > 0.4 with **BEP or CEP scores revealed enriched complement system and neurogenic proteins**

Discussion & Conclusion

- **Inflammation**, **fibrosis**, **angiogenesis**, and **neurogenesis** indicate a **chronic inflammation in MC2**
- The **inflammatory pathomechanism** in MC2 comprises **activation of the complement system**
- **Complement system** and **neoinnervation** may be linked to **endplate damage** (**Figure 4**)

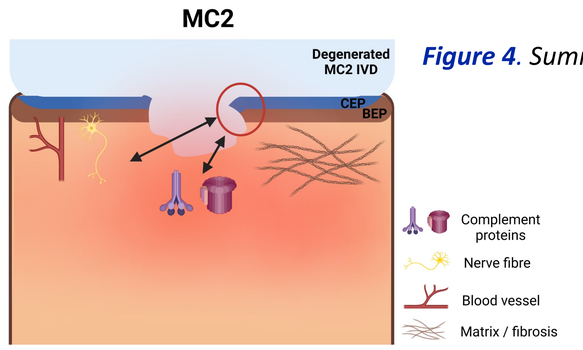
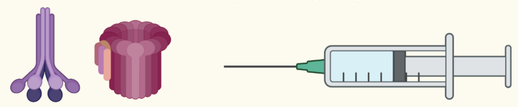


Figure 4. Summary

Implications

The **complement system** is linked to **tissue damage**, **angiogenesis**, **neurogenesis**, and **fibrosis**



The upregulated complement system in MC2 might be an interesting upstream target to control inflammation, progressive tissue damage, and further neurogenesis.

Reference: *1 Christine L Le Maitre et al. (2021). JOR Spine.*

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