Center of Experimental Rheumatology
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Higher Abundance of HTRA1 Generated Fragment Abundance in the Degradome of Modic Type 1 Discs

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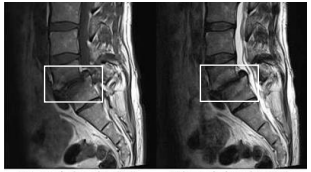
Introduction

Modic type 1 changes (MC1)



MC1 found adjacent to degenerated disc and damaged endplates

Compared to degenerated nonMC discs:

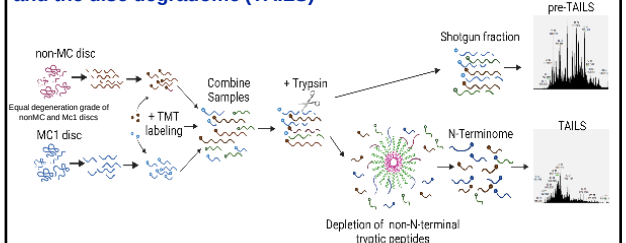
- MC1 discs degenerate faster
- MC1 discs have increased pro-inflammatory cytokines

We hypothesized that the MC1 discs contain more cleaved extracellular matrix (ECM) fragments and that they are generated through a MC1-specific mechanism.

Aims

(1) To determine if there are proteases and ECM fragments overrepresented in MC1 discs
(2) To test if these fragments act pro-inflammatory

Aim 1: Determine proteases of the MC1 disc (pre-TAILS) and the disc degradome (TAILS)



Aim 1: cont'd

- Shotgun proteomics identified HTRA1 as the only protease with increased abundance in the MC1 discs
- HTRA1-derived fragments are found increased in MC1 discs compared to nonMC discs (Fig. 1).
- N-TAILS found newly cleaved fragments more abundant in MC1 discs, indicating a difference in degeneration patterns (Fig. 2).
- The proteins producing most upregulated fragments were FN, COMP, COL1A1 and CILP1 (Fig. 3).
- In-vitro, HTRA1 cleaved recombinant CILP1, COMP and FN but not COL1A1.

Fig 1.: Median abundance of HTRA1 derived fragments in disc degradomes

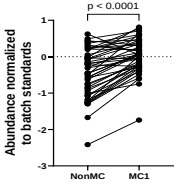


Fig 2.: N-Term peptide abundance

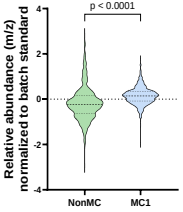


Fig. 3A: Degradome of MC1 vs. nonMC discs

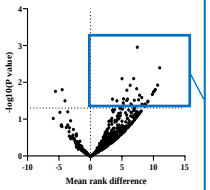
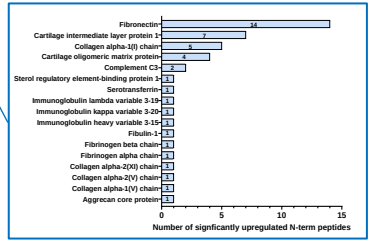
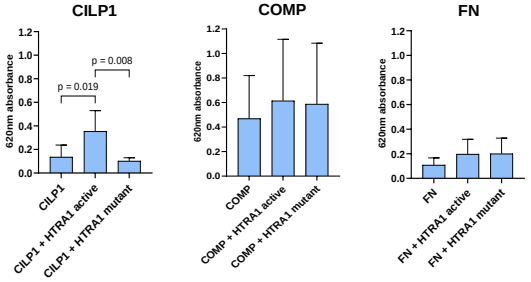


Fig 3B: N-Term peptides per protein with significantly increased abundance in MC1 discs



Aim 2: Determine inflammatory potential of HTRA1-derived fragments of CILP1, COMP and FN using THP1 NF-kB reporter cells



- HTRA1-cleaved CILP1 demonstrated a greater NF-kB response than full-length CILP1 or CILP1 with inactive mutant HTRA1.
- COMP induced an NF-kB response with both full-length and cleaved protein.
- FN did not induce an NF-kB response.

Conclusion

HTRA1 plays an important role in producing pro-inflammatory fragments like CILP1 fragments in MC1 discs.

Inhibiting HTRA1 may be a promising new treatment target.