Unique degeneration of intervertebral discs adjacent to Modic changes

POS0416

T. Mengis[1,2], I. Heggli[1,2], N. Herger[1,2], F. Brunner[2], M. Farshad[3], O. Distler[1,2], S. Dudli[1,2]

[1]Center of Experimental Rheumatology, Department of Rheumatology, University Hospital Zurich, University of Zurich, Switzerland,
[2]Department of Physical Medicine and Rheumatology, Balgrist University Hospital, University of Zurich, Switzerland,
[3]Department of Orthopedics, Balgrist University Hospital, University of Zurich, Switzerland

Background

Modic changes (MC) are painful vertebral bone marrow lesions and are often found in patients with chronic low back pain. The adjacent intervertebral disc (IVD) seems to play an important role: the rapidly degrading disc stands in an inflammatory cross-talk with the MC bone marrow and MC develop almost always simultaneously cranial and caudal to a degenerated IVDs. Few studies have investigated and reported differential expression of inflammatory cytokines and proteases by IVD cells adjacent to MC, however, how this affects the ECM degeneration has not been determined.

Objective

The aim of this study was to identify MC-specific cleavage of the extracellular matrix (ECM). We hypothesize that the 'Modic disc' has a distinct matrix degradome (Fig. 1).

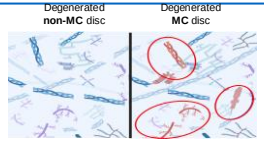

Fig. 1: *Hypothesized degradome of nonMC vs MC disc*

Methods

Degenerated lumbar IVDs from MC1 (n=29), MC2 (n=24) and non-MC (n=25) levels from gender and age matched patients undergoing spinal fusion surgery were collected. Degradome was measured with N-terminal amine isotopic labeling of substrates (TAILS) liquid chromatography tandem mass spectrometry (LC-MS/MS) (Fig. 3). TAILS allows to identify degraded proteins by detecting de novo N-terminal peptides. A standard comprised of 16 patients allowed normalization of all 6 batches to the standard. Differential abundance of peptides was determined using Mann-Whitney test comparing ranks of each peptide.

Results

Mean degree of disc degeneration as measured by Pfirrmann grade was not significantly different between groups (MC1: 3.8 ± 0.8, MC2: 4.1 ± 0.7, non-MC: 3.5 ± 0.7). Pre-TAILS comparable to a shotgun measurement of the disc detected a total of 833 peptides. The TAILS fraction, corresponding, measured a total of 1'111 different peptides. A subgroup of the TAILS peptides are the 638 peptides which correspond to the degenerative products through proteolytic cleavage in-vivo, identified by their N-terminal TMT label.

A total of 44 N-terminally labeled peptides, corresponding to in vivo cleaved protein fragments, were found upregulated in MC1 discs and 15 in MC2 discs (Fig.2). In the MC1 discs 14 of these peptides derive from fibronectin, 7 from cartilage intermediate layer protein 1 (CLIP1), 5 from collagen 1 (COL1A) and 4 from cartilage oligomeric matrix protein (COMP). Four of the fibronectin fragments found enriched in MC1 can be mapped to the 29kDa fibronectin region, a known DAMP. The exact same fragments found enriched from CILP1 and COMP have previously been identified in osteoarthritic tissue. The MC2 discs show enrichment for 14 N-terminal peptides belonging to 11 different proteins.

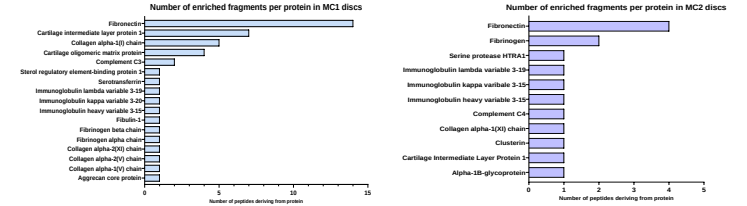

Fig. 2: *Number of N-terminally labelled peptides found more abundant in MC1 (top) and MC2 (bottom) discs per protein.*

Conclusion

The findings reveal a difference in the breakdown of the 'Modic discs' both in number of distinct fragments produced and in cleavage of these fragments. Further research will allow us to determine specifically which fragments play a role in the development of MC, finally presenting new treatment targets.

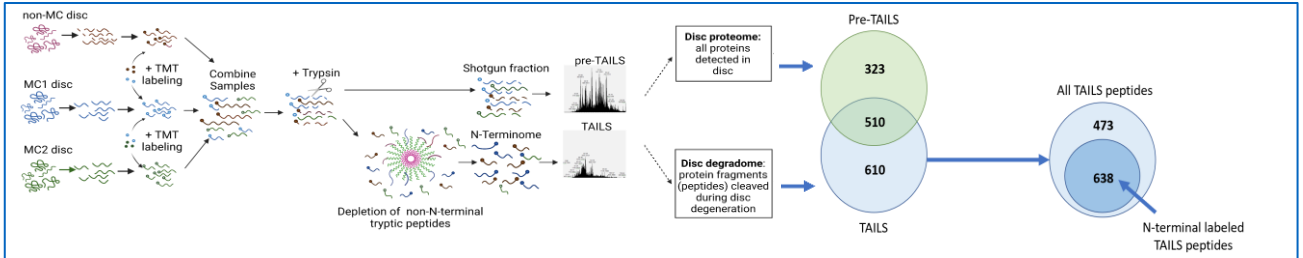

Fig. 3: *TAILS workflow for proteomic shotgun and N-terminome profiling of the MC1, MC2 and non-Modic discs. Venn diagram of peptides detected in pre-TAILS and TAILS measurement including overlaps followed by Venn diagram of TAILS peptides that have an N-terminal label and represent the de novo N-terminals.*

Universität Zürich[UZH] USZ Universitäts Spital Zürich balgristcampus Balgrist University Hospital