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**Title The articular cartilage proteome is dependent on zone, age and disease state**

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**Introduction** Osteoarthritis (OA) is a major chronic age-related musculoskeletal disease, leading to pain and disability. Cartilage deterioration during OA is principally initiated from the tissue, thus stratifying the anatomical regions of articular cartilage and investigating them separately could add a new level of understanding of OA leading to therapeutic targets.

**Materials and Methods** In this study we have divided donors into 3 groups: young (n=5, mean age=32), old (n=5, mean age = 71) and OA (n=5, mean age = 76). From each donor we collected superficial, middle and deep zones of knee articular cartilage using laser microdissection (LMD) technique, in total giving us 9 groups. Microdissected tissue was *in-situ* trypsin digested with the addition of RapiGest surfactant (Waters). Tryptic peptides from each samples were individually run using liquid chromatography-tandem mass spectrometry on an UltiMate 3000 Nano LC System coupled to a Q Exactive Quadrupole-Orbitrap instrument (Thermo Fisher). Progenesis™ QI for proteomics v4.0 was used for label-free quantification following protein identification using the Unihuman reviewed database in Mascot (Matrix Science), ANOVA values of p<0.05 and at least 2 unique peptides for protein identification were determined significant. Pathway analysis of differential abundant proteins was performed in IPA (Qiagen).

**Results** Using LMD an average for superficial zone 5mm2 of cartilage tissue was collected and for middle/deep zones 25mm2 area was collected. In total 514 proteins were identified in this study. Label-free quantification revealed differentially abundant proteins in groups by age, OA and zones. Pair wise comparison of differentially abundant proteins in the superficial zone between young and old group demonstrated the ‘activation of inflammatory response’ (p=7.47x10-6),’ inflammation of joint’ (p=3.42x10-6) and ‘apoptosis’ (p=6.96x10-5) pathways with ageing. Comparison of old and OA groups in this zone showed the ‘activation of apoptosis’ (p=8.63x10-6) and ‘cell death’ (p=9.28x10-9) in the OA group, whereas ‘inflammatory response’ (p=1.35x10-4) was upregulated in the old group. Similarly to the superficial zone, the ‘inflammation of joint’ (p=1.1x10-5) pathway was activated in the deep zone of old samples in comparison to young group. However, the deep zone OA group demonstrated the ‘activation of inflammatory response’ (p=4.94x10-4) in comparison to the old group. Old group in contrast had ‘activation in cell death’ (p=4.93x10-9) pathway.

**Discussion**: In the current study we have demonstrated a difference in protein abundance dependent on zone within articular cartilage, and that during ageing and OA these proteins change. From the results of pathway analysis we suggest that the proteome in the superficial and deep zones in ageing are similar, as old group had activated state of inflammation pathway in these two zones. However, comparing old and OA groups there are major differences between superficial and deep zones. It seems that at the protein level in OA cartilage inflammation pathways were downregulated in the superficial zone but activated in the deep zone when compared to the old group.