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Cellular and molecular mechanisms of subchondral bone sclerosis in hip osteoarthritis: the potential roles of multipotential stromal cells (MSCs) and osteocytes

Purpose: The cellular mechanism of subchondral bone changes in osteoarthritis (OA) is poorly understood. In hip OA, bone pathology is particularly evident in the MRI-defined BML areas, which are characterised by increased bone turnover and enhanced angiogenesis. Multipotential stromal cells (MSCs) are progenitors of osteoblasts and osteocytes. They also participate in bone resorption regulation by supporting blood vessel growth and producing osteoclast-activating RANKL and its inhibitor, OPG. We have previously documented increased numbers of CD271-positive MSCs in the BML areas of hip OA bone however they were defective in their mineralisation capacity, which suggested their potential contribution to bone pathology in these areas. The aim of this study was to investigate transcriptional and topographic relationships between MSCs and osteocytes in healthy and OA bone, and in relation to osteochondral damage in this disease.

Methods: Femoral heads were removed following total hip arthroplasty for late stage OA (N=14) while healthy cancellous bone was obtained from the iliac crest of trauma patients (N=7). Bone samples were used for histological staining with Haematoxylin & Eosin or Safranin O or digested with collagenase to release cells, which were subsequently stained with antibodies against CD271 and CD45 to purify bone-resident MSCs (CD45-CD271+ cells). Sorted populations as well as donor-matched osteocyte-pure bone were analysed for gene expression by qPCR. Selected molecules were confirmed by immunohistochemistry on EDTA-decalcified femoral heads.

Results: In both healthy and OA bone, osteocytes expressed significantly more SOST, DMP1 and PHEX (late osteocytes markers) compared to MSCs, whereas DKK1 and E11 (early osteocyte markers) were less differentially-expressed. Compared to healthy cancellous bone, OA MSCs were characterised by higher-level expression of ALP and OPG (3- and 4-fold, respectively, $p<0.05$). OA osteocytes expressed 9-fold more of PDPN (the early osteocyte marker encoding E11 protein), 4-fold more osteocyte collagenase MMP14 and 5-fold more OPG (all $p<0.05$). By immunohistochemistry, E11-positive 'early' osteocytes were particularly numerous in the most damaged areas of OA femoral heads, characterised by a breached osteochondral junction, the thinnest cartilage and the largest subchondral bone area. E11-positive osteocytes were juxtaposed to cuboid bone-lining osteoblasts and CD271-positive MSCs and had numerous and disorganised dendrites (Figure 1). This active bone formation process was particularly notable in the subchondral areas where the fibrovascular tissue containing CD271-positive MSCs and blood vessels had breached the tidemark.

Conclusions: This is the first study to document gene expression signatures of native osteocytes and MSCs in human cancellous bone. Secondly, it shows that in late-stage hip OA bone, both MSCs and osteocytes are characterised by gene expression signature favouring bone formation and inhibition of bone resorption. These data provide a mechanistic explanation for subchondral bone sclerosis in hip OA and propose that subchondral bone MSCs should be a target for novel therapy development. An early correction of their abnormal migration and osteogenesis bias could prevent an excessive bone formation and the corresponding cartilage destruction in this disease.

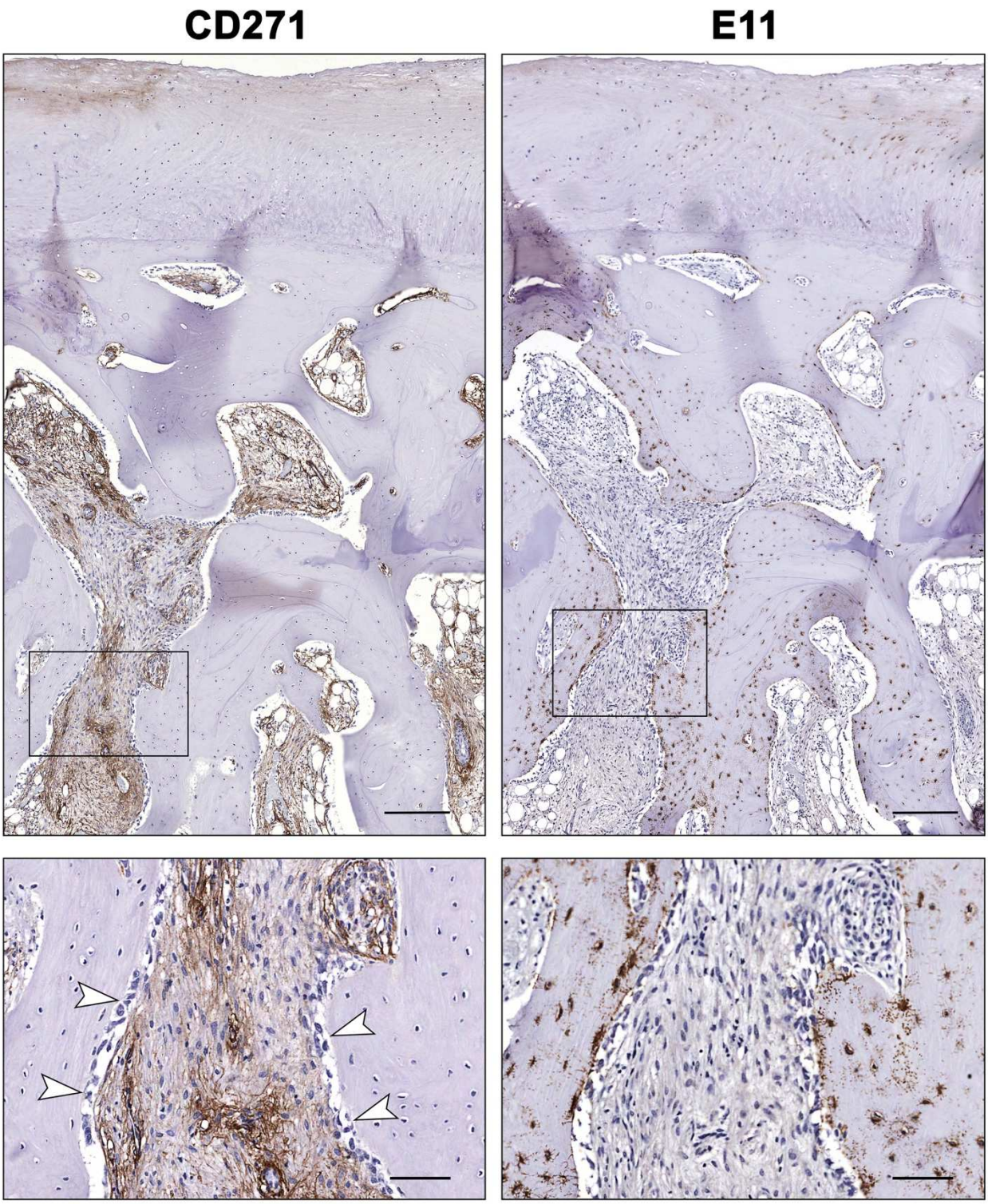

Figure 1: Immunohistological staining of OA femoral head.
Osteochondral area showing the association between the CD271+MSCs in the invading fibrovascular tissue and the high density of E11osteocytes in the adjacent newly formed bone.
Square: selection of the bottom panel; Arrow heads: Osteoblasts; Scale bar: 200μm top panel; 50μm bottom panel