Cellular and molecular mechanisms of bone sclerosis in hip osteoarthritis – the potential roles of a novel CD271+/CD56+ multipotential stromal cell population

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Rationale: The cellular mechanism of subchondral bone sclerosis in osteoarthritis (OA) is poorly understood. An altered bone architecture has been particularly observed directly under the damaged cartilage or in MRI-defined bone marrow lesions (BMLs), the latter being predictive of OA progression [1]. Subchondral bone changes, as the disease progresses, are now evident in hip [1], knee [2] and ankle OA [3], indicating that these alterations are a universal OA feature.

Aim: The aim of this study was to investigate gene expression profiles and topographical changes in bone -lineage cells with MSC phenotypes in OA bone compared to healthy and osteoporotic bone. Furthermore, we sought to define a novel population of MSCs immediately juxtaposed to the bone surface.

Methods: Femoral heads were removed following total hip arthroplasty for late stage OA or osteoporotic fragility fracture while healthy cancellous bone was obtained from the iliac crest of trauma patients. Bone samples were used for histological analysis or digested with collagenase to release all bone-resident cells, which were subsequently stained with antibodies against CD271, CD45, CD56 and CD146 to identify different MSC subsets. Sorted populations as well as bone-embedded, pure osteocytes were analysed for their gene expression by qPCR.

Results: Compared to healthy cancellous bone, OA femoral head bone was characterised by higher-level expression of osteoblast- and anti-resorption related genes, in both MSCs (CD45-CD271+ cells) and native osteocytes. Increased expression of alkaline phosphatase was observed in CD271+ MSCs, while osteoprotegerin (OPG) as well as OPG/RANKL ratio was increased in both native osteocytes and CD271+ MSCs. Compared to healthy bone, CD56+ bone-lining cells were significantly increased in OA femoral heads (medians of 0.46% and 3% of CD45-CD271+ cells, respectively) and particularly concentrated near the osteochondral junction in the areas of active bone remodelling (in the vicinity of osteoclasts and osteoblasts) (Fig.1A). This CD271+CD56+ MSC subset displayed an increased expression of osteogenesis-related genes, including RUNX2, SP7/Osterix, BGLAP/Osteocalcin and SPP1/Osteopontin compared to control CD271+CD146+CD56- population (Fig.1B), indicating its pre-osteoblast nature.

Conclusions: Late-stage, femoral head OA bone contains increased numbers of osteogenically-committed CD271+CD56+ MSCs, and mesenchymal-lineage gene expression signature favouring bone formation rather than bone resorption. These data provide a mechanistic explanation for OA subchondral bone sclerosis and propose that future therapeutic interventions aimed at restoring normal bone homeostasis in OA should target these bone-lining MSCs.

Reference: 1. Bowes, M.A., et al., Ann Rheum Dis,2016; 2. Burr, D.B., Gallant, M.A., Nat Rev Rheumatol.,2012; 3. Nakasa T, et al., Foot Ankle Int.,2014

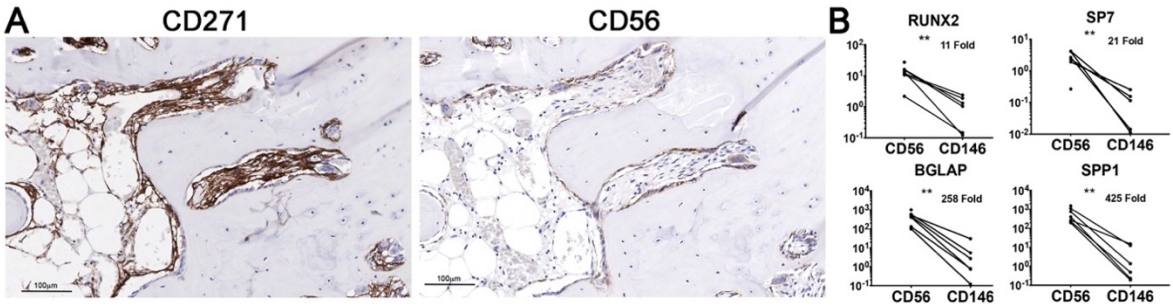

Figure 1Figure 1: A. MSCs appearance in OA subchondral bone showing positive staining in perivascular (arrow heads) and bone lining (arrows) locations. B. Relative gene expression levels normalised to HPRT1 of the key osteogenic molecules and median fold changes.