Intrinsic multipotential mesenchymal stromal cell activity in gelatinous Heberden’s nodes in osteoarthritis at clinical presentation

Thomas G Baboolal1, Sally A Boxall1, Sarah M Churchman1,2, Conor T Buckley3, Elena Jones1,2 and Dennis McGonagle1,2*

Abstract

Introduction: Gelatinous Heberden’s nodes (HNs), also termed synovial cysts, are a common form of generalized osteoarthritis (OA). We sought to determine whether HN cases at clinical presentation contained multipotential stromal cells (MSCs) and to explore whether such cells were more closely related to bone marrow (BM) or synovial fluid (SF) MSCs by transcriptional analysis.

Methods: At clinical presentation, gelatinous material was extracted/extruded from the distal phalangeal joint of OA patients with HNs. From this, plastic adherent cells were culture-expanded for phenotypic and functional characterization and comparison with BM- and SF-MSCs. Mesenchymal related gene expression was studied by using a custom-designed TaqMan Low Density Array to determine transcriptional similarities between different MSC groups and skin fibroblasts.

Results: In all cases, HN material produced MSC-like colonies. Adherent cultures displayed an MSC phenotype (CD29+, CD44+, CD73+, CD81+, and CD90+ and CD14− CD19−, CD31−, CD34−, CD45−, and HLA-DR−) and exhibited osteogenic, chondrogenic lineage differentiation but weak adipogenesis. Gene cluster analysis showed that HN-MSCs were more closely related to SF- than normal or OA BM-MSCs with significantly higher expression of synovium-related gene markers such as bone morphogenic protein 4 (BMP4), bone morphogenetic protein receptor type 1A (BMPR1A), protein/leucine-rich end leucine-rich repeat protein (PRELP), secreted frizzled-related protein 4 (SFRP4), and tumor necrosis factor alpha-induced protein 6 (TNFAIP6) (P <0.05).

Conclusions: Gelatinous HNs derived from hand OA at clinical presentation contain a population of MSCs that share transcriptional similarities with SF-derived MSCs. Their aberrant entrapment within the synovial cysts may impact on their normal role in joint homeostasis.

© 2014 Baboolal et al.; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
trials to date have used MSCs to treat OA (search terms “mesenchymal stem cells” AND “osteoarthritis” [6]). We originally identified a population of MSCs in knee synovial fluid (SF) and observed their increase in early knee OA [7]; similarly, increases are also reported following joint injury [8,9]. It is speculated that mobilization of MSCs from the synovium into the SF is a response to tissue injury, suggesting that SF-MSCs play a role in joint homeostasis [9,10]. There is also good evidence that, under a corrected mechanical environment, using joint distraction, cartilage regeneration can be achieved without direct manipulation of the synovial compartment [11,12], again suggesting that the joint has the intrinsic capacity to restore and remodel OA-associated pathology [13]. Given that HNs are associated with new bone formation and that the constituents of the gelatinous material are similar to SF [2,14], we hypothesized whether HN cysts contain a population of MSCs similar to those found in other synovial joints.

Although ossified HNs are common, early manifestations with gelatinous material are infrequent and rarely present to the clinician at a stage when they can be aspirated [1,2]. We undertook cellular and transcriptional evaluation of culture-expanded cells from patients with gelatinous HNs at clinical presentation and compared those cells with MSCs derived from OA SF and BM from OA and normal patients. Herein, we show that such patients with early HNs have an MSC population entrapped within these cysts.

Methods
Collection of gelatinous material from Heberden’s nodes
We identified three female patients (ages 44 to 66 years) with painful distal interphalangeal (DIP) joint HNs. All imaging and samples were collected following informed written consent under ethics approved by the Leeds East NHS Research Ethics Committee. Patients had conventional x-ray of their hands prior to sample collection (Figure 1A). HNs were punctured aseptically with a 16-gauge needle; gelatinous material within was extruded from the joint (Figure 1A) and collected in 5 mL of saline.

Cell isolation and culture expansion
Extruded HN material was diluted (1:4) with non-hematopoietic (NH) expansion medium (Miltenyi Biotec, Bisley, UK), centrifuged, and resuspended in NH medium. Samples were plated in triplicate and cultured for 14 days with twice-weekly media changes in NH medium before counting colonies; these cells were considered passage 0 (p0). Thereafter, colonies were trypsinised (0.25% trypsin; Invitrogen, Paisley, UK) and further expanded. For expansion, cells were seeded at a density of $10^4$ cells per cm$^2$, with twice-weekly media changes, and further grown to between p1 and p3. For comparative analysis, MSCs were also expanded from OA knee SF aspirates as described above for HN cells (SF, n = 5 donors) and normal and OA BM. Briefly, normal iliac crest BM (ICBM) (n = 11) was aspirated from orthopedic patients undergoing elective surgery for the removal of metalwork. BM from OA patients—osteoarthritic femoral canal BM (OAFCBM) (n = 3)—was aspirated from the medullary canal at the neck of the femur during hip arthroplasty [15]. Plastic adherent cells from normal and OA BM were expanded as for NH cells. Additionally, MSCs were isolated from osteoarthritic femoral head BM (OAFHB) (n = 3). Femoral heads from hip arthroplasty of patients with OA were mined by using a bone mill. Bone fragments were washed in phosphate-buffered saline, and cells were enzymatically extracted with collagenase as previously described [16]. For ethical reasons, BM could not be collected from the iliac crest of patients with OA. Patients were between 39

![Figure 1 Sample collection, cell growth, and multipotential stromal cell characterization.](image-url)
and 76 years old. All cells were seeded and expanded as above. Primary fibroblast (FB) lines CRL-2068 and HFF1 (ATCC, Teddington, UK) and NHDF (Lonza, Basel, Switzerland) were purchased and grown similarly. Growth kinetics for HN cells was compared with SF- and ICBM-MSCs by calculating the population doubling rate (PDR) between p0 and p1 by using the following equation: 

$$\text{PDR} = \frac{\text{days in culture/population doubling (PD)}}{\text{PD} = \log_2 (\log \text{cells harvested/log cells seeded}).}$$

Hierarchical cluster analysis of quantitative polymerase chain reaction (qPCR) data was log2-transformed and filtered (filter = 80% present), resulting in 88 out of 96 genes analyzed. Complete linkage analysis was performed and dendrograms were generated by using Cluster 3.0 software and Java TreeView version 1.1.6 [19,20]. Statistical analysis (Mann-Whitney U) was performed by using SPSS 20 (IBM Inc., Portsmouth, UK).

### Results

**Gelatinous material from Heberden’s node contains multipotential stromal cell-like cells**

Similar to control SF and ICBM [17], MSC-like cells were isolated and expanded from the gelatinous material from the DIP joint HNs of all three patients (Figure 1A and B). After 14 days of proliferation and from approximately 0.5 mL of gelatinous material, four, 16, and 42 colonies were present from the three patient samples. With further expansion after p0, HN cells continued to grow at rates similar to SF- and ICBM-derived MSCs (Figure 1C). Each HN culture was taken to at least p2, corresponding to approximately 15 to 20 population doublings (PDs). This was equivalent to approximately 1 PD every two days, consistent with our previously reported results for SF- and ICBM-MSCs [7].

**Trilineage potential of Heberden’s node cells**

Trilineage differentiation was performed on culture-expanded (p2-3) cells (Figure 2A). Pellets formed in chondrogenic medium stained positive for sulphated-GAGs, consistent with SF and ICBM controls and indicative of progression toward the chondrogenic lineage. HN cells cultured in osteogenic medium exhibited strong alizarin red staining, similar to SF-derived MSCs but less than those derived from ICBM, indicating that cells were committed to an osteogenic lineage. In contrast to SF- and ICBM-MSCs, all HN samples tested demonstrated weak staining for adipogenesis, with only isolated cells having an accumulation of micro-vesicles (Figure 2A).

**Culture-expanded cells from Heberden’s node have a multipotential stromal cell phenotype**

Flow cytometry was used to determine the immunophenotype of expanded HN cells and compared with SF- and ICBM-derived MSCs. HN cells were uniformly negative for CD14, CD19, CD31, CD34, CD45, and HLADR (Figure 2B). Consistent with an MSC phenotype, HN cells were uniformly positive for CD29, CD44, CD73, CD81, and CD90 (Figure 2B). This immunophenotype was similar to culture-expanded SF- and ICBM-MSCs.
Figure 2 Multipotential stromal cell (MSC) differentiation and immunophenotyping. (A) Representative images show trilineage differentiation capacity of Heberden’s node (HN)-MSCs compared with synovial fluid (SF)- and iliac crest bone marrow (ICBM)-MSCs. Adipogenesis of HN-MSC was low, and only micro-vesicles were observed (insert). (B) Plot showing mean percentage of populations positive for cell surface markers by flow cytometry (n = 3 for HN-, SF- and ICBM-MSCs). Error bars represent standard deviation. Below are example histogram overlays of Heberden’s node (blue), synovial fluid (green), and bone marrow (red) MSCs with isotype control (grey-filled).
Quantitative real-time polymerase chain reaction shows Heberden's node-MSC are transcriptionally related to synovial fluid-MSC

To further characterize HN-MSCs, qPCR was performed by using transcripts that reflect the stromal origin and trilineage potential of MSCs [19]. Hierarchical cluster analysis was used to determine similarities in expression patterns between HN-, SF-, OAFCBM-, and OAFHBM-MSCs (all from patients with established OA) as well as MSCs from normal ICBM and primary FBs (Figure 3). MSCs derived from OA patient BM were used to control for potential differences in expression patterns between normal and OA BM. All MSC samples clustered away from FBs on a separate branch, confirming that gene expression profiles were cell type-specific (for MSCs). HN-MSCs clustered together with SF-MSCs, whereas all BM-derived MSCs clustered as a distinct group away from SF- and HN-MSCs (Figure 3). This clustering of SF- and HN-MSCs shows a similar transcriptional profile, indicating that these cells may share a common niche-specific origin and that the expressions of these genes were not related to OA.

Examples of differentially expressed genes between MSCs and FBs are shown in Figure 4A and Table 1. These data confirmed ICBM-MSC specificity for these genes as reported in our previous study [19] and extend this to SF- and HN-MSCs, suggesting MSC specificity for these genes regardless of the tissue of origin. Additionally, we identified genes differentially expressed between MSCs from the joint and BM (Figure 4B and Table 2). Significantly, a common niche identity for both HN- and SF-MSCs was clearly seen within this set of genes as increased expression of transcripts known to be associated with synovial MSCs, such as bone morphogenic protein 4 (BMP4), bone morphogenic protein receptor type 1A (BMPRIA), protein/leucine-rich end leucine-rich repeat protein (PRELP), secreted frizzled related protein 4 (SFRP4), and tumor necrosis factor α-induced protein 6 (TNFAIP6) [9,21-23].

Our data also identified increases in the expression of genes associated with chondrogenesis for both HN- and SF-MSCs over BM-derived MSCs (Figure 4B and Table 2), including aggrecan (ACAN); bone morphogenetic protein
4 (BMP4) and cartilage oligomeric matrix protein (COMP) [22,24]. Taken together, these data indicated a potential common origin/synovial niche specificity for HN- and SF-MSCs.

**Discussion**

Acute HNs are a feature of pre-radiographic hand OA and these gelatinous synovial cysts are thought to be a forerunner of new bone formation [1-4]. The nature of the gelatinous material (being rich in hyaluronan [2,14]) and the new bone formation that occurs in OA at these locations lead us to the hypothesis that MSCs may become entrapped from the joint SF in such material in the earliest stages of OA. Herein, we show the presence of HN resident cells which met functional, phenotypic, and transcriptional profiles of MSCs that are closely related to SF-MSCs [9,19].

Although HNs are a common form of generalized nodal OA, clinical presentation at the acute phase, prior to ossification, is somewhat rare; only three cases have appeared in our clinic in the past five years [1,3]. Consequently, only a small number of such gelatinous cysts could be sampled. Despite these low sample numbers, the functional, phenotypic, and transcriptional data presented here are consistent with these cells being MSCs. There was, however, a surprising difference in the capacity of the HN-MSCs to differentiate toward the adipogenic lineage. Functional assays showed only isolated cells with the accumulation of micro-vesicles in each donor, despite the expression of the adipogenic transcription factors CEBPA (CCAAT/enhancer-binding protein) and PPRAG. A lack of adipogenesis has been linked to ‘in vitro’ aging of MSCs, whereby the ability of cells to differentiate is reduced as the cells approach senescence [25,26]. Owing to the prolonged culture expansion period needed to expand HN-MSCs to sufficient numbers to complete our functional, phenotypic, and expression assays, our cells may have been approaching senescence, which has reduced their capacity to differentiate toward the adipogenic lineage.
### Table 1 Common multipotential stromal cell genes

| Gene                     | HN/FB | SF/FB | ICBM/FB |
|--------------------------|-------|-------|---------|
| ACVR2A                   | 2.8   | 3.5   | 7.0     |
| ANGPT1                   | 5.3   | 4.6   | 4.9     |
| BAMBI                    | 18.2  | 36.8  | 10.2    |
| CDH11                    | 11.4  | 8.8   | 9.0     |
| COL1A1                   | 15.3  | 4.3   | 6.0     |
| COL1A2                   | 20.2  | 20.8  | 9.9     |
| CXCL12                   | 3.1   | 5.4   | 1.9     |
| EPHB4                    | 5.5   | 2.3   | 2.6     |
| FZD1                     | 4.7   | 11.5  | 4.6     |
| GDF5                     | 73.5  | 4.04  | 25.5    |
| GJA1                     | 8.2   | 14.7  | 10.2    |
| HAPLN1^a                 | 397.3 | 258.5 | 691.3   |
| IGFBP3                   | 59.5  | 107.8 | 5.1     |
| MYH9^a                   | 6.0   | 6.0   | 6.8     |
| PAPSS2                   | 2.8   | 5.1   | 2.7     |
| RUNX1                    | 3.0   | 59.0  | 1.9     |
| SFRP4                    | 171.2 | 908.9 | 4.8     |
| SORT1                    | 4.4   | 8.9   | 11.1    |
| SPARC                    | 7.0   | 7.0   | 7.1     |
| VEGFC                    | 3.1   | 10.2  | 1.6     |

Relative fold change in expression compared with fibroblasts (FBs) \((P \leq 0.05, \text{Mann-Whitney } U)\). ^aNewly identified genes. HN, Heberden’s node; ICBM, normal iliac crest bone marrow; SF, synovial fluid.

### Table 2 Tissue-specific multipotential stromal cell genes

| Gene                     | HN/ICBM | SF/ICBM | HN/SF  |
|--------------------------|---------|---------|--------|
| ACAN                     | 12.5    | 15.6    | 0.8    |
| ALPL                     | 4.8     | 6.4     | 0.8    |
| BMP2                     | 3.1     | 20.8    | 0.1    |
| BMP4                     | 3.2     | 5.6     | 0.6    |
| BMPR1A                   | 3.8     | 4.3     | 0.9    |
| CEBPA                    | 11.4    | 19.1    | 0.6    |
| COMP                     | 17.2    | 10.8    | 1.6    |
| DAAM2                    | 2.9     | 2.2     | 1.4    |
| FZD4                     | 13.4    | 7.5     | 1.8    |
| GATA2                    | 7.1     | 9.4     | 0.7    |
| IGFBP3                   | 11.8    | 21.3    | 0.6    |
| OMD                      | 7.8     | 32.0    | 0.2    |
| PPARG                    | 79.9    | 14.0    | 5.7    |
| PRELP                    | 19.1    | 87.1    | 0.2    |
| SFRP4                    | 35.7    | 189.6   | 0.2    |
| TFAP6                    | 33.4    | 97.8    | 0.3    |
| UGDH                     | 2.1     | 3.1     | 0.7    |

Relative fold change in expression identified as diagnostic for synovial fluid/Heberden’s node-multipotential stromal cells (SF/HN-MSCs) from statistical analysis \((P \leq 0.05, \text{Mann-Whitney } U)\). ICBM, normal iliac crest bone marrow.
Differential transcriptional analysis has previously been shown to reliably distinguish MSCs from FBs and subdivide MSCs from their tissue of origin by identifying commonly expressed genes when cells are grown at the same conditions [27-30]. Here, we used a similar experimental approach and confirm our previous findings [19], indicating mesenchymal lineage-specific expression of genes on our custom array (Table 1). We verified that FZD1 (frizzled family receptor 1), IGFBP3 (insulin-like growth factor-binding protein 3), PAPSS2 (3′-phosphoadenosine 5′-phosphosulfate synthase 2), and VEGFC (vascular endothelial growth factor C) are differentially expressed between MSCs and FBs [30] and also newly identify genes differentially expressed between MSCs and FBs such as GDF5 (growth differentiation factor-5) and HAPLN1 (hyaluronan and proteoglycan link protein 1), which are involved in skeletal development, cartilage formation, and maintenance [24,31]. Further to defining the HN cells as MSCs, our transcriptional analysis indicates that these MSCs share a gene-specific expression profile more comparable to SF-MSCs. We compared HN- and SF-MSCs not only with normal ICBM-MSCs but also with BM from OA patients. For ethical reasons, OA BM could not be collected from the iliac crest of these patients. Rather, MSCs were derived from two sources: (a) the medullary canal of the femur and (b) trabecular bone of femoral head from OA patients all undergoing hip arthroplasty. We have previously described these MSCs as functional and phenotypic indistinct from their ICBM counterparts [15,16]. Such analysis allowed joint/BM-specific differences to be identified rather than differences relating to OA. Among genes expressed by HN- and SF-MSCs (but downregulated in BM-MSCs) were the recently identified marker of synovium MSCs, SFPFR4 [9], and several genes known to be associated with cartilage formation and maintenance, such as ACAN, BMP4, PRELP, and TNFIP6 (Figure 4 and Table 2) [22,24,31,32]. To fully confirm the tissue origin of MSCs in vivo and to establish their migration patterns following injury or in disease, lineage tracing experiments in animal models are required [33]. Nevertheless, our transcript data as well as previous findings [27-30] indicate that broad tissue or niche-specific transcriptional profiles are maintained in culture and as such can be informative on the MSC ‘in vivo’ functionality in a given environment.

With both normal human and animal joints having resident SF-MSCs [17], it is possible that HN-MSCs are entrapped from SF extruded through sites of weakness in the joint capsule [34] and that, like the knee, small joints contain a resident SF-MSC population. Previous gene profile analysis indicates that SF-MSCs in turn originate from the adjacent synovium [8,9], and our data suggest a similar origin for HN-MSCs based on transcriptional analysis. Our data cannot exclude the possibility that HN-MSCs are BM-derived but transcriptionally ‘altered’ following their entrance into the joint environment; this is, however, unlikely as no damage to bone and hence the entry route for these MSCs can be identified at this early stage of OA. We therefore conclude that, similar to SF-MSCs, HN-MSCs are most likely of synovial origin. Although HNs are forerunners of new bone formation, no significant osteogenic bias was seen in any HN-MSC cultures (either by qPCR or differentiation assay); this may be explained by the fact that, in this study, HN material was collected early in disease, prior to ossification. As such, our data suggest that these MSCs are unlikely to have intrinsic osteogenic bias, perhaps with the aberrant new bone formation seen in HNs a result of subsequent alterations in joint biomechanics.

Conclusions
We present the first description of MSCs in a small joint at a stage when cartilage damage is minimal (as seen by x-ray; Figure 1A). Future clinical studies will be needed to establish whether these MSCs are mere “bystanders” or in fact contribute to the aberrant remodeling and subsequent ossification seen during disease progression. Conversely, these MSCs may represent an intrinsic joint repair process that is abolished by cyst entrapment and altered biomechanics. The identification of MSCs within another as-yet-unexplored synovial compartment is further indication that joint-specific MSCs may be important for joint homeostasis [5,35]. Additional studies on the biology of SF-MSCs and whether these cells contribute to spontaneous joint repair are critical. The presence of these resident MSCs may also offer a distinct therapeutic advantage. Perhaps it may be possible to control disease progression and elicit effective joint repair by identifying patients earlier in disease, and correcting the underlying biochemical or biomechanical instability prior to ossification.

Abbreviations
ACAN: aggrecan; BM: bone marrow; BMP4: bone morphogenetic protein 4; DIP: distal interphalangeal; FB: fibroblast; FITC: fluorescein isothiocyanate; HN: Heberden’s node; ICBM: iliac crest bone marrow; MSC: multipotent stromal cell; NH: non-hemopotetic; OA: osteoarthritis; OAFHB: osteoarthritic femoral head bone marrow; p: passage; PD: population doubling; PDR: population doubling rate; PE: phycocyanin; PRELP: proline/arginine-rich end leucine-rich repeat protein; qPCR: quantitative polymerase chain reaction; SF: synovial fluid.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
TB participated in the design of the study, drafting of the manuscript, and interpretation of the results; shared responsibility for data acquisition; and helped to perform data analysis. EJ participated in the design of the study, drafting of the manuscript, and interpretation of the results and helped to perform data analysis. DM participated in the design of the study, drafting of the manuscript, and interpretation of the results. SB, SC, and CB shared responsibility for data acquisition. All authors critically evaluated the manuscript and read and approved the final version.
Acknowledgments

We thank Stuart Calder, Rahul Singh, and Peter Giannoudis, who supported our research by providing synovial fluid and bone marrow samples. This work was funded through WELMEC, a Centre of Excellence in Medical Engineering funded by the Wellcome Trust and EPSRC, under grant number WT 089082/2/09Z. SB was supported by PurStem - FP7 project number 225398. SC is supported by the NIHR-Leeds Musculoskeletal Biomedical Research Unit.

Author details

1 Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Chapel Allerton Hospital, Chapleltown Road, Leeds LS7 4SA, UK. *NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospital NHS Trust, Chapel Allerton Hospital, Chapleltown Road, Leeds LS7 4SA, UK.
2 Trinity Centre for Bioengineering, Trinity Biomedical Sciences Institute, Trinity College Dublin, 152-160 Pearse Street, Dublin 2, Ireland.

Received: 18 December 2013 Accepted: 23 May 2014
Published: 3 June 2014

References

1. Kellgren JH, Moore R: Generalized osteoarthritis and Heberden’s nodes. Br Med J 1952, 1:181–187.
2. Jackson DG, Kellgren JH: Hyaluronic acid in Heberden’s nodes. Ann Rheum Dis 1957, 16:238–240.
3. Rees F, Doherty S, Hui M, Maciewicz R, Muir K, Zhang W, Doherty M: Distribution of finger nodes and their association with underlying radiographic features of osteoarthritis. Arthritis Care Res 2012, 64:533–538.
4. Thaper A: Relationship between Heberden’s nodes and underlying radiographic changes of osteoarthritis. Ann Rheum Dis 2005, 64:1214–1216.
5. Barry F, Murphy M: Mesenchymal stem cells in joint disease and repair. Nat Rev Rheumatol 2013, 9:584–594.
6. ClinicalTrials.gov homepage. [http://clinicaltrials.gov/]
7. Jones EA, English A, Henshaw K, Markham AF, Emery P, McCrindle E, Doherty M, Emery P: Synovial fluid increase in the knee with degenerated cartilage and inflammatory and degenerative arthritis. Arthritis Rheum 2004, 50:811–827.
8. Monto T, Muneta T, Hara K, Yu YJ, Mochizuki T, Makino H, Umezawa A, Sekiya I: Synovial fluid-derived mesenchymal stem cells increase after intra-articular ligament injury in humans. Rheumatology (Oxford) 2008, 47:1137–1143.
9. Sekiya I, Ojima M, Suzuki S, Yamaga M, Horie M, Koga H, Tsujl K, Miyaguchi K, Oshima S, Tanaka H, Umezawa A, Sekiya I: Mesenchymal stem cells derived from synovium, meniscus, anterior cruciate ligament, and articular chondrocytes share similar gene expression profiles. J Orthop Res 2009, 27:393–400.
10. Dijoud F, Bomy C, Häuptl T, Uzd G, Lahbou N, Louis-Pence F, Apparailly F, Canovas F, Rême T, Sany J, Jorgensen C, Neill D: Transcriptional profiles discriminate bone marrow-derived and synovium-derived mesenchymal stem cells. Arthritis Rheum 2005, 51:1304–1315.
11. Intema F, Van Roermund PM, Marijnissen AC, Cotofana S, Eckstein V, Ansorge W, Ho AD: Characterization of mesenchymal stem cells in health and early osteoarthritis: detection and functional evaluation at the single-cell level. Arthritis Rheum 2010, 62:7171–7170.
12. Vanarell D, Buckley CT, Thorpe SD, Kelly DJ: Composition-function relations of cartilaginous tissues engineered from chondrocytes and mesenchymal stem cells isolated from bone marrow and infrapatellar fat pad. J Tissue Eng Regen Med 2011, 5:873–883.
13. Churchman SM, Ponchel F, Bixall SA, Cuthbert R, Kouroupis D, Rosshdy T, Giannoudis PV, Emery P, McDonagh D, Jones EA: Transcriptional profile of native CD271+ multipotential stem cells: evidence for multiple fates, with prominent osteogenic and Wnt pathway signalling activity. Arthritis Rheum 2012, 64:2632–2643.
14. Eisen MB, Spellman PT, Brown PO, Botstein D: Cluster analysis and display of genome-wide expression patterns. Proc Natl Acad Sci U S A 1998, 95:14863–14868.
15. Segawa Y, Muneta T, Makino H, Nimura A, Mochizuki T, Yu YJ, Ezura Y, Umezawa A, Sekiya I: Mesenchymal stem cells derived from synovium, meniscus, anterior cruciate ligament, and articular chondrocytes share similar gene expression profiles. J Orthop Res 2009, 27:393–400.
16. Herlofsen SR, Kührer AM, Melvick JE, Brinchmann JE: Chondrogenic differentiation of human bone marrow-derived mesenchymal stem cells in self-gelling alginate discs reveals novel chondrogenic signature gene clusters. Tissue Eng Part A 2011, 17:1003–1013.
17. Wagner W, Bork S, Horn P, Kricun D, Walenda T, Diehlmann A, Benes V, Blake J, Huber F-X, Eckett V, Boukamp P, Ho AD: Aging and replicative senescence have related effects on human stem and progenitor cells. PLoS One 2009, 4:e8546.
18. Bani A, Muraglia A, Dozin B, Magrociaco M, Cancetta R, Quarto R: Proliferation kinetics and differentiation potential of ex vivo expanded human bone marrow stromal cells: implications for their use in cell therapy. Exp Hematol 2000, 28:707–713.
19. Wagner W, Wein F, Seckinger A, Frankhauser M, Winkler U, Krause U, Blake J, Schwager C, Eckett V, Ansorge W, Ho AD: Comparative characteristics of mesenchymal stem cells from human bone marrow, adipose tissue, and umbilical cord blood. Exp Hematol 2005, 33:1402–1416.
20. Ishii M, Koike C, Igarashi A, Yanamaka K, Pan H, Higashi Y, Kawaguchi H, Sugiyama M, Kamata N, Iwata T, Matsubara T, Nakamura K, Kurihara H, Tsujl K, Kato Y: Molecular markers distinguish bone marrow mesenchymal stem cells from fibroblasts. Biochem Biophys Res Commun 2005, 332:297–303.
21. Breidel C, Küklick L, Hartmann O, Kim TD, Boudriot U, Schwell D, Neubauer A: Distinct gene expression profile of human mesenchymal stem cells in comparison to skin fibroblasts employing cDNA microarray analysis of 9600 genes. Gene Exp 2005, 12:435–437.
22. Kubo H, Shimizu M, Taya Y, Kawamoto T, Michida M, Kaneko F, Igarashi A, Nishimura M, Segoshi K, Shimazu Y, Tsujl K, Asba T, Kato Y: Identification of mesenchymal stem cell (MSC)-transcription factors by microarray and knockdown analyses, and signature molecule-marked MSC in bone marrow by immunohistochemistry. Genes Cells 2009, 14:407–424.
23. Coleman CM, Tuan RS: Functional role of growth/differentiation factor 5 in chondrogenesis of limb mesenchymal cells. Mech Dev 2003, 120:823–836.
24. Pei M, He F, Vunjak-Novakovic G: Synovium-derived stem cell-based chondrogenesis. Differentiation 2008, 76:1044–1056.
25. Kurth TB, Delfaccio F, Crouch V, Augello A, Sharpe PT, De Bari C: Functional mesenchymal stem cells niches in adult mouse knee joint synovium in vivo. Arthritis Rheum 2011, 63:1289–1300.
34. Tan AL, Grainger AJ, Tanner SF, Shelley DM, Pease C, Emery P, McGonagle D. High-resolution magnetic resonance imaging for the assessment of hand osteoarthritis. *Arthritis Rheum* 2005, 52:2355–2365.

35. De Bari C, Kurth TB, Augello A. Mesenchymal stem cells from development to postnatal joint homeostasis, aging, and disease. *Birth Defects Res C Embryo Today* 2010, 90:257–271.

doi:10.1186/ar4574

Cite this article as: Baboolal et al: Intrinsic multipotential mesenchymal stromal cell activity in gelatinous Heberden’s nodes in osteoarthritis at clinical presentation. *Arthritis Research & Therapy* 2014 16:R119.