The underlying molecular regulators and their effects on mineralisation in the trabecular bone microenvironment and osteoblast of primary hip osteoarthritis

Duminda Dananjaya Kumarasinghe (BBiotech, Hons)

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The Discipline of Pathology
School of Medical Sciences
Faculty of Health Sciences
The University of Adelaide
South Australia
Australia
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**Thesis abstract**

Primary hip osteoarthritis (OA) is emerging as a dynamic pathology, developing over a long period and involving many tissue types of the joint, including the bone. Previous studies have established differential gene expression, changes in microarchitectural indices, altered cellular characteristics and material properties in the bone of primary hip OA. These studies suggest that OA is a systemic disease involving the bone and validate the assessment of molecular changes to further investigate this complex disease. The aim of the studies herein was to further characterise the altered gene expression profile in both OA bone and osteoblasts, and compare these with control (CTL) bone and cells, respectively. The first study examined differential gene expression, histomorphometric indices and relationships between these, in femoral trabecular bone from OA patients and CTL subjects, with the aim of identifying molecular changes consistent with structural and remodelling indices in the OA pathology. The second and third studies used primary osteoblasts derived from female hip OA cases against CTL to investigate the expression of candidate OA disease genes during osteoblast differentiation and mineralisation, in terms of calcium apposition and elemental composition of the mineral.

A number of alterations in gene expression, histomorphometric indices and correlations were identified in OA bone compared to CTL. Notably, significant relationships observed in CTL bone between critical components of the Wnt/β-catenin signalling pathway (e.g. CTNNB1) and regulators of osteoblastogenesis (e.g. TWIST1) with indices of bone formation and structure were absent in OA bone. Conversely, the expression of MMP25, a regulator of matrix degradation, and indices of bone resorption were correlated exclusively in OA.

In the second study fundamental differences in osteoblast behaviour were identified in cells cultured *ex vivo* from OA bone. The Ca:P ratio was significantly more varied in OA compared to CTL. Calcium apposition and mineral composition changed significantly
over time. Genes associated with osteoblast differentiation were analysed with respect to the mineral measures. TWIST1 mRNA expression was elevated and correlated with SMAD3 mRNA levels in the OA cohort during the time course. Associations were observed between TNAP, OCN, TWIST1, TGF\(\beta\)1, SMAD3 mRNA levels and mineral measures in OA against CTL. Temporal differences between SMAD3 mRNA expression and mineral composition were also found in OA.

The third study concerned genes involved directly with the regulation of osteoblast/osteocyte mediated mineralisation. Analysis revealed that PHEX and PTEN mRNA expression were higher and more varied in OA. PHEX mRNA expression correlated with PTEN throughout the time course in OA cultures, both genes also correlated with Ca apposition. Other OA-specific patterns of gene correlations were identified, including those between MEPE and OCN, and MEPE and DMP1. Additionally, associations between gene expression and mineral measure were significantly different in OA; including those between MEPE and Ca apposition, as well as the Ca:P ratio, DMP1 and the Ca:P ratio, and PTEN and the Ca:C and P:C ratios.

Together, these findings suggest that inherent molecular changes in the bone and importantly, its constituent osteoblasts, contribute to the pathology of primary hip OA. These studies strongly imply that at least in the case of primary hip OA, the bone should be considered as an important contributor to the disease aetiology. The differentially expressed molecules identified herein associated with microarchitectural and compositional changes offer avenues for further experimental investigations and, potentially, novel therapeutic targets.
Declaration

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Duminda D. Kumarasinghe
Statement of Authorship

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Rheumatology 2011; 50(12): 2166-2175

KUMARASINGHE, D.D. (Candidate)
Reviewed and assessed papers, interpreted findings, prepared draft manuscript and acted as corresponding author.

I hereby certify that the statement of contribution is accurate:

Signed

.................................Date

HOPWOOD, B.
Supervised work, helped with interpretation and manuscript evaluation.

I hereby certify that the statement of contribution is accurate:

Signed

.................................Date

KULIWABA, J.S.
Supervised work, helped with interpretation and manuscript evaluation.

I hereby certify that the statement of contribution is accurate:

Signed

.................................Date

ATKINS, G.J.
Supervised work, helped with interpretation and manuscript evaluation.

I hereby certify that the statement of contribution is accurate:

Signed

.................................Date
FAZZALARI, N.L.

Supervised work, helped with interpretation and manuscript evaluation.

I hereby certify that the statement of contribution is accurate:

Signed... ........................................Date................................. 21/12/2011
Statement of Authorship

Critical molecular regulators, histomorphometric indices and their correlations in the trabecular bone in primary hip osteoarthritis

Osteoarthritis and Cartilage 2010; 18(10): 1337-1344

KUMARASINGHE, D.D. (Candidate)

Performed data analysis on all samples, interpreted data, wrote manuscript and acted as corresponding author.

I hereby certify that the statement of contribution is accurate:

Signed ........................................Date. 6/12/11

PERILLI, E.

Assisted with data interpretation and manuscript evaluation.

I hereby certify that the statement of contribution is accurate:

Signed... ........................................Date. 6/12/11

TSANGARI, H.

Assisted with data analysis and manuscript evaluation.

I hereby certify that the statement of contribution is accurate:

Signed..... ........................................Date. 7/12/11

TRUONG, L.

Assisted with data analysis and manuscript evaluation.

I hereby certify that the statement of contribution is accurate:

Signed..... ........................................Date. 3/12/11

x
KULIWABA, J.S.

Supervised development of work, helped in data interpretation and manuscript evaluation.

I hereby certify that the statement of contribution is accurate:

Signed...........................................Date...6/12/11

HOPWOOD, B.

Assisted with data analysis, supervised development of work, helped in data interpretation and manuscript evaluation.

I hereby certify that the statement of contribution is accurate:

Signed.. ...........................................Date.......1/12/11

ATKINS, G.J.

Supervised development of work, helped in data interpretation and manuscript evaluation.

I hereby certify that the statement of contribution is accurate:

Signed...........................................Date.......4/12/11

FAZZALARI, N.L.

Supervised development of work, helped in data interpretation and manuscript evaluation.

I hereby certify that the statement of contribution is accurate:

Signed...........................................Date......21/12/2011
Statement of Authorship

Evidence for the dysregulated expression of TWIST1, TGFβ1 and SMAD3 in differentiating osteoblasts from primary hip osteoarthritis patients

Osteoarthritis & Cartilage 2012: submitted

KUMARASINGHE, D.D. (Candidate)

Performed analysis on all samples, analysed and interpreted data, wrote manuscript.

Certification that the statement of contribution is accurate:

Signed. ..................................................Date. 27/02/12...

SULLIVAN, T.

Assisted with data analysis and manuscript evaluation.

Certification that the statement of contribution is accurate and permission is given for the inclusion of the paper in the thesis:

Signed... ..................................................Date. 29/02/12...

KULIWABA, J.S.

Supervised work, helped with interpretation and manuscript evaluation.

Certification that the statement of contribution is accurate and permission is given for the inclusion of the paper in the thesis:

Signed... ..................................................Date. 29/02/12...

FAZZALARI, N.L.

Supervised work, helped with interpretation and manuscript evaluation.

Certification that the statement of contribution is accurate and permission is given for the inclusion of the paper in the thesis:

Signed...... ..................................................Date. 28/02/2012
ATKINS, G.J.

Supervised work, helped with interpretation and manuscript evaluation and acted as corresponding author.

Certification that the statement of contribution is accurate and permission is given for the inclusion of the paper in the thesis:

Signed... .........................................Date.../\/\/
Statement of Authorship

Altered expression and association with mineral composition of PHEX, MEPE and DMP1 in osteoblasts from primary hip osteoarthritis

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KUMARASINGHE, D.D. (Candidate)

Performed analysis on all samples, analysed and interpreted data, wrote manuscript.

Certification that the statement of contribution is accurate:

Signed ..........................................Date 12/06/12

FAZZALARI, N.L.

Supervised work, helped with interpretation and manuscript evaluation.

Certification that the statement of contribution is accurate and permission is given for the inclusion of the paper in the thesis:

Signed.. ........................................Date 10/6/2012

ATKINS, G.J.

Supervised work, helped with interpretation, manuscript evaluation and acted as corresponding author.

Certification that the statement of contribution is accurate and permission is given for the inclusion of the paper in the thesis:

Signed ........................................Date 12/06/12
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Publications


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**Prizes and awards**

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Honourable mention in the Hanson Institute South Australian Research News, 2008

The Healthy Aging Research Cluster Best Poster Prize, 2008

The Healthy Aging Research Cluster Best Poster Prize, 2007

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