Mapping Early Bone Marrow Lesion and Pain Development in Spontaneous and Load-induced mouse models of OA

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What is osteoarthritis (OA)?

OA is a disease characterised by multiple soft and mineralised joint tissue changes, which have relationships that remain unresolved

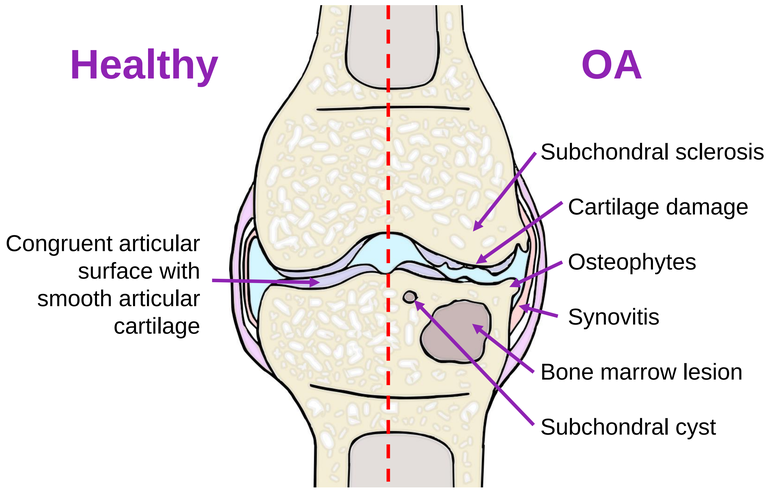

Figure 1. Features of healthy (left) compared to OA joint (right)

Bone Marrow Lesions in OA

- Subchondral cysts (SCC) related to knee OA pain onset[1]
- Histology of human SCC can only provide late OA snapshot[2]
- Complementary MRI has charted clinical disease longitudinally[3,4]

…little is known about initiation and early progression of SCC

STR/ort mice develop OA spontaneously and exhibit knee SCC (Fig. 2), making them an ideal model in which to characterise histological, cellular and molecular features underpinning these early phases

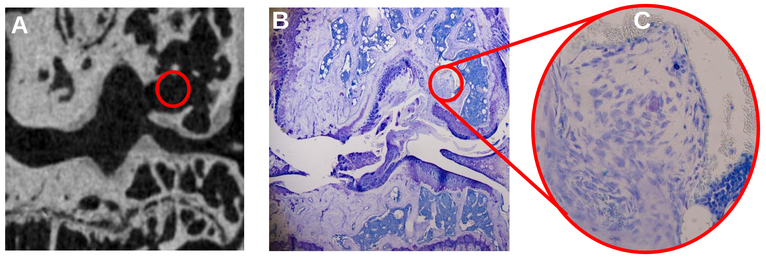

Figure 2. Coronal sections of STR/ort mouse knee showing an SCC (circled): A. on micro-computed tomography (µCT), B. a histological section stained with Toluidine blue, and C. the same SCC enlarged[5]

Aims and hypotheses

Characterise the temporal emergence of SCC and their spatial relationship to cartilage lesions in ageing STR/ort mice with increasing OA severity

Hypothesis: that SCC will increase in prevalence, number and volume with increasing age and OA grade, and will be closely aligned with the OA-prone sites of articular cartilage on the medial tibial plateau of STR/ort mouse joints

Methods and work flow

A cross-sectional approach will be used to describe SCC development within 3 groups of OA-prone male STR/ort mice aged to 8-12, 20 and 40+ weeks corresponding to pre-onset, early and advanced OA, and in age-matched, non-prone female and control parental (CBA) mice.

1. Left hindlimb selection (from archived samples):

Strain	Sex	Age (weeks) and OA stage		
		8-12 pre-OA	20 OA-onset	40+ late-OA
STR/ort	♂	n=9	n=9	n=9
	♀	-	-	n=2
CBA	♂	-	-	n=2

Figure 3. Number of limbs per group

2. Knee joint imaged by µCT for SCC volume measurement

3. Limbs dissected, decalcified, wax-embedded (A) and sectioned (B) for histological staining with Toluidine blue (C)

4. Microscopy used to ascertain SCC prevalence, number and location and to score cartilage lesions

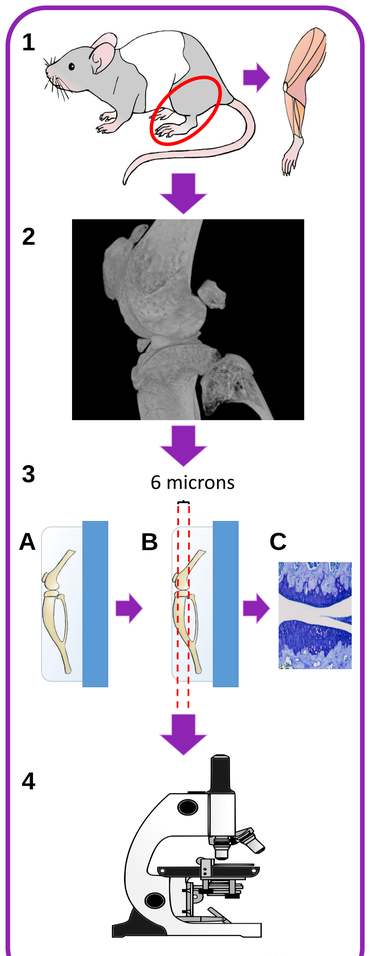

Figure 4. Workflow[6]

In-cyst on progress

- This work is part of a larger study funded by Versus Arthritis which will use the STR/ort mouse as a model of both bone marrow lesions (BML) and SCC which are temporally & spatially related (Figure 5)[4]

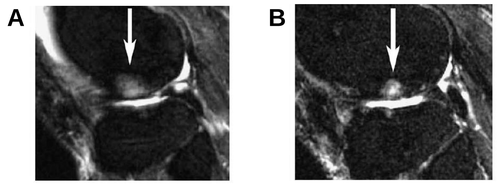

Figure 5. Paired sagittal MRI images (T2 weighted fat saturated) of human OA knee showing: **A**. BML (arrowed, hyperintense diffuse area) and **B**: 12.5 months later, an SCC (arrowed, round hyperintense focal area)[4]

- Unmet clinical need to understand BML/SCC onset and progression at a histological, cellular and molecular level and relationship to pain

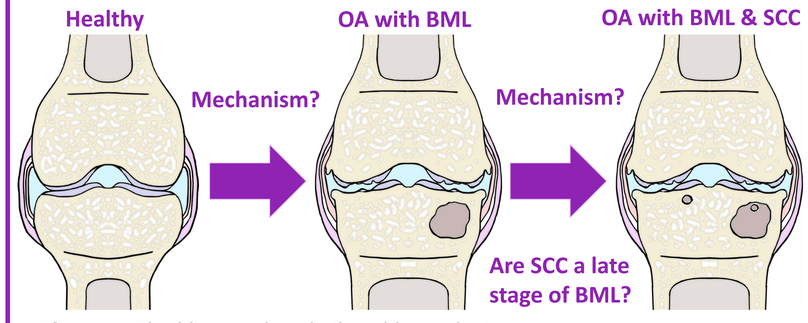

Figure 6. The big questions in the wider project

- Follow on studies will explore relationships between BML, SCC and pain using MRI, µCT, histology, blood and tissue molecular markers
- Identification of new markers of early, sub-clinical OA will allow earlier diagnosis, provide understanding of factors that drive OA onset and progression and provide new therapeutic targets

References

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[3] Carrino, J. A. et al. (2006) Osteoarthr Cartil, 14(10), 1081-5.
[4] Crema, M. D. et al. (2010) Radiol, 256(3), 855-62.
[5] Images provided by B. Javaheri with permission.
[6] Image 3 histological section from Poulet, B. (2010) Unpublished thesis (Ph.D.), The Royal Veterinary College, University of London.