Reviewer's report

Title: Type X collagen levels in serum are elevated in human Osteoarthritis and associated with markers of cartilage degradation and systemic inflammation

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Reviewer: Jessica Bertrand

Reviewer's report:

In their manuscript “Type X collagen levels in serum are elevated in human Osteoarthritis and associated with markers of cartilage degradation and systemic inflammation” the authors He et al., describe their findings on the detection of collagen X fragments in serum of OA patients. The authors correlated in their study the presence of collagen fragments with radiological OA severity (Kellgren score), as well as hsCRP as a marker for inflammation and C2M as a marker for collagen 2 degradation.

The topic of this study is of great importance, because until now we have no reliable serum or urine marker to detect OA severity or predict OA progression in patients. We lack especially marker for early OA. Therefore it is remarkable that the authors see differences in collagen X fragmentation already at Kellgren 2.

The authors show in their study that collagen X fragments increase in serum at Kellgren 2, but did not see any further significant increase with higher Kellgren scores. Furthermore, they found that collagen X fragments correlated with hsCRP and C2M. They did not find this correlation between C2M and hsCRP.

He et al. conclude from their data that chondrocyte hypertrophy is associated with inflammation and cartilage degradation.

Major compulsory revisions:

For me, this study is highly interesting and I congratulate the authors to their findings. However, I am not completely convinced of the conclusion the authors draw from their study.

1.) I propose that the authors either do the additional experiments I have proposed in the “discretionary revisions” section, or change their conclusion to: …. Chondrocyte hypertrophy and subsequent collagen X fragmentation seems to increased in a subset of patients with inflammatory OA….. I think it is important to highlight here that this seems to be typical for patients with inflammation driven OA and might not be true for all OA types.

2.) It did not become clear for me, whether the shown histological stainings are from patients of the cohort, or separate samples and how they are connected to the cohort. Can the authors please clarify this in the manuscript?

3.) IgG control figure 5A shows a positive staining surrounding the chondrocytes. Please include another control or staining
Minor essential revisions:

1.) There is a typo in the methods section in the description of collagen X staining in cartilage biopsies: 370C and 600C # which should read 37°C and 60°C

Discretionary Revisions:

To really nail down that hypertrophy is a result of inflammation and that this can be measured via collagen X fragments I propose a few simple additional experiments.

I suggest following experiments:

1.) bovine explant cultures or murine hip caps of healthy cartilage (as the epitope is conserved in these species and the antibody should be able to detect the fragments) # treated with IL-1

2.) bovine explant cultures or murine hip caps of healthy cartilage # dose response of IL-1 and/ or time course to show specificity of the process

3.) bovine explant cultures or murine hip caps of healthy cartilage # induction of hypertrophy in this system using thyroxin

4.) bovine explant cultures or murine hip caps of healthy cartilage # combination of thyroxin and IL-1 in combination

As a read out I propose the detection of collagen X fragment as well as C2M.

Level of interest: An exceptional article

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I have no competing interests