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Spontaneous hypertensive rat exhibits bone and meniscus phenotypes of osteoarthritis: is it an appropriate control for MetS-associated OA?

The potential roles of metabolic syndrome (MetS) in the onset and progression of osteoarthritis (OA) have been a hot topic in the field since it may potentially open up to new non-surgical treatment regimens. To better study the relationship between MetS and OA, a suitable animal model would be a vital tool in understanding the pathomechanism and also for screening and testing various potential drug candidates.

We have recently read Deng and colleagues' letter entitled 'Eplerenone treatment alleviates the development of joint lesions in a new rat model of spontaneous metabolic-associated osteoarthritis' published online this May, which mentioned the use of 'obese spontaneously hypertensive heart failure' (SHHF$^{cp/cp}$) rat model to study MetS-associated OA and chronic administration of eplerenone, a mineralocorticoid receptor antagonist, as a treatment.[1] While we appreciate the authors' dedicated effort, we believe there are several issues concerning the novel animal model that are worth mentioning.

MetS is a cluster of at least three out of five of the following conditions: central obesity, hypertension, hyperglycaemia, high cholesterol levels and low high-density lipoprotein levels. Since it is a complex medical condition, we were very much intrigued by the authors' choice to study the mixed components of MetS in one model rather than studying the effect of the individual components. This study design does indeed allow the authors to look into potential synergistic effects of the MetS components; the major flip side is that up to this moment neither are the weights of the individual components contributing to MetS-associated OA known nor are all these components as well studied as obesity and also hyperglycaemia. One component in MetS that we would like to highlight here is hypertension. We believe that there is still a huge research gap in the relationship between hypertension and MetS-associated OA to warrant an independent study. To put this into context, in the latest Framingham osteoarthritis study, Niu and colleagues observed that after adjustment for weight or body mass index, all metabolic syndrome components except hypertension have no significant association with the occurrence of OA.[2] In other words, hypertension is highly likely a key factor in the pathogenesis of MetS-associated OA although little is known about the mechanism behind.

As we congratulate the authors' accomplishment in successfully developing the MetS strain reported in a previous publication which does indeed check three of the five boxes ("ie," dyslipidemia, hypertension and obesity), we are reserved about the use of spontaneously hypertensive rat (SHHF+/+) for the control group. While we understand the rationale behind choosing this strain, we think it is far from an optimal control since it is still unclear whether the hypertensive background itself may exert any effects on the joint structure and it has been previously suggested that hypertension on its own may play a role in the onset and progression of OA.[3 4] Indeed in our recent study, we did observe significant changes in bone and menisci by 9 months including the presence of subchondral cyst-like giant voids near the anterior cruciate ligament (ACL) enthesis and increased ossified tissue volume of the menisci in the spontaneously hypertensive rat with the Wistar Kyoto strain as the default normotensive control (figure 1).[5]

We cannot help but think that the authors seem to have regrettably overlooked the significance of hypertension in this study and we are very interested in learning from their response regarding the above issues.

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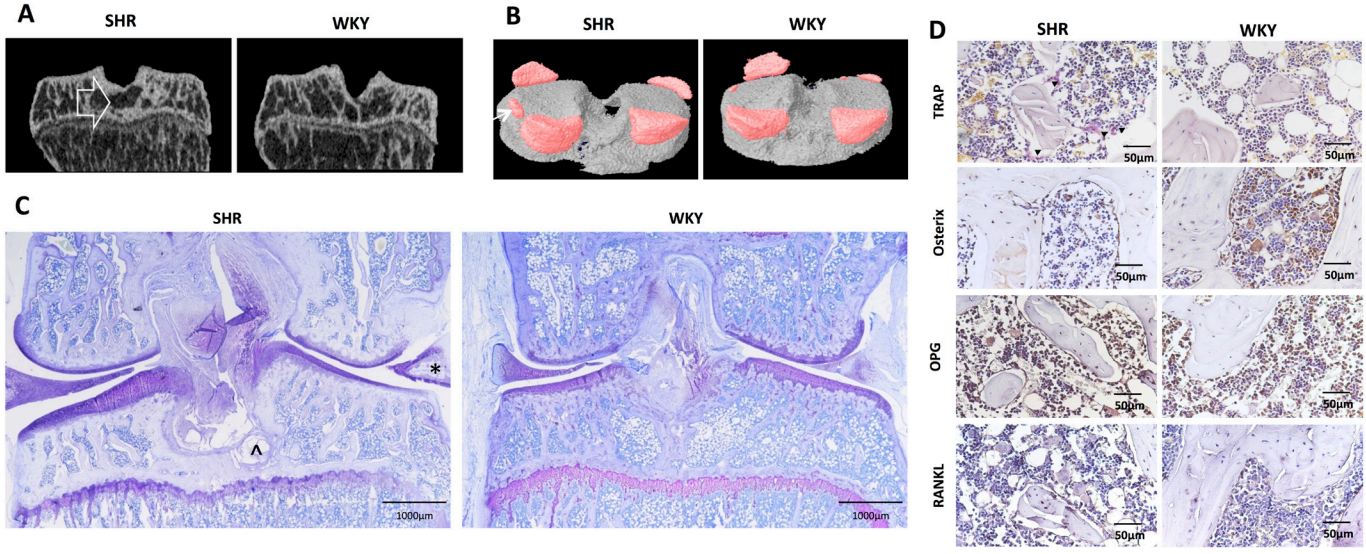

Figure 1 Osteoarthritis-like changes in 9-month-old spontaneously hypertensive rats (SHR). (A) SHR model exhibited subchondral bone cyst (block arrow) yet the control Wistar Kyoto strain (WKY) rats did not have it. (B) The menisci ossification was much more pronounced in the middle portion of the medial meniscus (arrow) in the SHR model. (C) All these micro-CT findings were echoed by histopathological examination (^, subchondral bone cyst; *, menisci ossification). (D) Uncoupled subchondral bone remodelling in SHR was characterised by increased tartrate-resistant acid phosphatase+ (TRAP+) osteoclasts but decreased Osterix+ osteoprogenitors. It was possibly due to elevated receptor activator of nuclear factor kappa-B ligand (RANKL) expression level relative to osteoprotegerin (OPG) expression level.

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