Given the known natural aging process, should preclinical experiments be designed longitudinally to determine whether a specific order of joint tissues is associated with the onset of pathological changes?

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Response: Yes. While it is clear that age exacerbates both the incidence of OA pathology and the experience of chronic joint pain, how specific tissues contribute to OA pain and how age affects this relationship is largely unknown. As such, preclinical studies aimed at identifying age-related mechanisms of OA pain should consider multiple joint tissues across all osteoarthritic models, and evaluate the whole joint at timepoints representing both the onset of OA pain and established OA pain, whenever feasible.

Level of Evidence: Weak to moderate

Methodology: A pubmed search was conducted using the following terms “pain AND aging AND osteoarthritis AND (mouse OR mice OR rat)”. This search yielded 150 papers. Upon review, 64 of these 150 papers conducted a behavioral assay of pain or investigated nervous system physiology (i.e. brain imaging, gene expression in the DRG, staining of joint innervation). Further, only 17 of the 64 identified studies used aged animals (defined as greater than 12 months for the purposes of this review): 7 studies in rats and 10 studies in mice. Still, some of the remaining 47 studies did explore tissue specific drivers of OA pain and are discussed in the summary below.

Findings:

Relationship between Joint Remodeling and OA Pain in the Preclinical Model: Clinically, there is a long-standing discordance between the radiographic severity of OA pathology and patient reports of OA pain severity[1; 2], leading many to postulate that OA pain mechanisms either extend beyond the joint or occur below the resolution of current medical imaging techniques. Here, preclinical studies can help illuminate mechanistic changes that occur in different joint tissues and how these changes relate to the development of OA pain (as measured through behavioral assays). Still, the combined results of our search indicated a lack of consensus across the field, mirroring clinical data on the relationship between joint remodeling and the severity of OA symptoms. For example, in a mouse mechanical joint loading model, mechanical hypersensitivity correlated with cartilage lesion severity, but not synovitis[3]; note, this study did not evaluate the underlying bone. Most other studies tend to indicate relationships between OA pain-related behaviors and either bony remodeling[4; 5] and/or synovitis[6-8], including our own work in the rat medial meniscus transection model[9-11]. Importantly, many of these studies demonstrate that modulation of bone remodeling and synovitis can augment OA pain, even in the absence of an effect on cartilage health[6; 7; 12]. Together these studies suggest that while cartilage, bone, and synovial changes each contribute to OA pain, their relative contributions may vary by model and disease stage, and that structural damage and pain do not always track together in a simple linear fashion.

Nervous System Changes in Preclinical OA Models: Expanding beyond joint tissues, a number of studies have investigated how OA-associated pain is driven by changes in the peripheral and central nervous systems. Here, multiple groups have shown strong evidence of OA-related neuro-inflammation in the lumbar dorsal root ganglia,[13-18] with these activation patterns influenced by the age of the animal.[14] Changes in nociceptive fiber density, including the innervation growth across the osteochondral boundary[19; 20], has also been observed in multiple joint tissues.[21] Other preclinical studies have provided direct evidence for central nervous system involvement in OA pain, including changes in gray matter volume, BOLD signal, and functional connectivity in the brain.[22; 23] Importantly, these changes may be modulated by both age and sex during OA progression, with widespread network recruitment in early-phase OA potentially contributing to pain chronification.[24] Taken together, these studies paint a picture of OA pain involving substantial shifts in physiology both within and beyond the joint, with aging amplifying these changes at multiple levels of the neural system.

Preclinical Studies Evaluating OA Pain and Aging: As noted above, we found less than 20 studies that investigated the role of aging on OA pain development in a preclinical rodent model, and many of these studies did not evaluate specific tissues sources for OA pain. Across all studies, age appears to contribute to the severity of OA pain, with the effect sizes in behavioral assays generally being larger in middle-aged or aged rodents compared to young animals[25; 26]. Again, these studies can be grouped by those investigating joint-level mechanisms and mechanisms that extend beyond the joint. Regarding joint tissues, multiple recent studies have evaluated the role of senescent cells in chronic joint pain, with strong evidence that age-related changes in autophagy and mitochondria function relate to age-related OA pain. Here, in multiple rodent models of knee OA, the administration of a senolytic drugs was able to reduce OA-related thermal and mechanical hypersensitivity.[6; 27] Moreover, intra-articular delivery of senescent cells was sufficient to induce pain and impaired mobility in mice without OA, providing some causal evidence for a role of cellular senescence in age-related joint pain.[28] In addition to direct modulation of cellular senescence, a few studies have modulated age-related changes in metabolism, with concurrent effects on pain measures.[29-31] Regarding nervous system involvement, brain remodeling in pain- and emotion-related regions of the brain has been documented with post-traumatic OA in aged rats[22], in MIA-induced OA in aged rats[24], and in MIA-induced OA in aged mice[23; 32]. At the level of the DRG, aged mice show immune remodeling consistent with age-related increases in immune activation, which also correlated to worsened allodynia and hyperalgesia.[14] Combined, these studies show strong evidence for the role of aging in the development of OA related pain, but the timing of pathological changes in different tissues is not evident and may be dependent on the type of OA model that was used.

Recommendations: Combined, these studies show strong evidence for multiple tissues being involved in OA-related pain and that aging-related factors contribute to the incidence and severity of OA-related pain. Given the historic disconnect between OA pathology and OA pain and the known contribution of age to the incidence and severity of OA, studies that investigate age-related contribution to OA pathology and OA pain are of strong interest to the field. However, conducting these studies on a tissue specific basis is highly complex and often infeasible. We recommend the strong consideration of effects across the entire joint and to physiologic systems that extend beyond the joint in studies of age-related OA pain when feasible, but we recognize that the broad longitudinal characterization of all tissues involved in OA pathology and OA pain is likely impractical for most current preclinical studies. We also recommend the evaluation of OA pathology and pain at timepoints that represent both the onset of OA pain and established OA pain, whenever feasible.

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