Q12: Does aging alter communication between joint tissues (e.g., cartilage and subchondral bone, fat and cartilage, fat and bone, synovium and cartilage)? Are there interactions that need to be standardized?

Kelsey H. Collins, Hope D. Welhaven, Kyle Allen, Kevin G. Burt, Chia-Lung Wu, Rachel E. Miller, Natalia S. Harasymowicz, Tristan Maerz, Tamara Alliston

RESPONSE/RECOMMENDATION:
YES. Aging plays a significant role in altering communication between joint tissues, contributing to osteoarthritis (OA) progression[1]. Cellular senescence, chronic inflammation ("inflammaging"), and reduced regenerative capacity associated with aging disrupt homeostatic interactions among joint components like cartilage, bone, adipose tissue, meniscus, and synovium. These changes create a catabolic, inflammatory environment that accelerates tissue degeneration. Aging also alters cellular responses (e.g., autophagy and repair) and tissue composition (e.g., cartilage stiffening, fibrosis), impacting mechanobiology and tissue communication. While animal models are crucial for probing mechanisms in a dynamic system, they have translational limitations. In vitro systems, such as tissue-on-a-chip models, offer controlled environments to study interorgan crosstalk but may oversimplify complex processes. Collaborative, interdisciplinary, and multi-modal approaches are essential for addressing these challenges and advancing targeted therapies for OA in aging populations.

LEVEL OF EVIDENCE: Strong. A Pubmed search was completed for "interorgan crosstalk," "joint tissues," "osteoarthritis," and "aging" was performed and the findings are summarized below.

Cartilage and Subchondral Bone: Aging profoundly affects the crosstalk between cartilage and subchondral bone, which is critical for maintaining joint integrity[2, 3]. Aging alters bone remodeling in the subchondral region, leading to sclerosis, microstructural changes, and impaired mechanical support for overlying cartilage. Concurrently, aged cartilage exhibits reduced anabolic signaling, heightened catabolic activity (via matrix metalloproteinases and aggrecanases), and increased susceptibility to mechanical stress. The altered biomechanical and biochemical signaling between these tissues exacerbates cartilage degeneration and contributes to OA progression.

Fat and Cartilage: Intra-articular and periarticular fat depots house resident immune cells and play a crucial role in maintaining joint homeostasis by producing adipokines, which regulate cartilage metabolism[4-10]. Aging disrupts this balance, for example, with senescent adipocytes secreting increased levels of pro-inflammatory adipokines (e.g., leptin[5, 10-12], resistin[13, 14]), reduced levels of protective factors such as adiponectin[13, 15], and increased fibrosis[16, 17]. In addition to adipokines, lipid profiles in synovial fluid are associated with OA severity and synovitis[18-21] in both animal models and humans. These changes and resulting secreted pro-inflammatory mediators from the fat pad can promote cartilage catabolism and synovial inflammation, further driving OA progression - but the mechanisms remain unclear.

Fat and Bone: The interaction between fat and bone is also altered with aging, particularly in the context of bone marrow adiposity. Aging increases bone marrow fat accumulation, which negatively affects osteoblast differentiation and bone formation. Simultaneously, adipocyte-derived inflammatory mediators exacerbate subchondral bone sclerosis and impair the bone-cartilage interface, likely contributing to OA progression, through mechanisms that remain to be defined. It is understood that adipose-secreted factors play a critical role in bone homeostasis and sclerosis, but the order in which these changes occur, and what is protective vs pathological, remains unclear.

Synovium and Cartilage: The synovium, which regulates joint lubrication and nutrient supply to cartilage, adopts a pro-inflammatory and pro-fibrotic phenotype with aging. Synovial fibroblasts exhibit disease-associated diversification in aging and during OA progression[22, 23], and the expansion of a senescent synovial fibroblast phenotype is associated with aging[24, 25], characterized by the secretion of inflammatory cytokines (e.g., IL-6, IL-1β), pro-fibrotic factors (e.g. TGF-β), neutrotrophic factors (e.g. NGF), and matrix-degrading enzymes (e.g. MMP-

3, -9), which amplify cartilage degradation. The crosstalk between synovium and cartilage represents a self-accelerating cascade in which synovitis-mediated cartilage breakdown accelerates synovitis via overactivation of innate inflammation; this inflammation further drives the secretion of catabolic enzymes and cytokines that orchestrate cartilage degradation. Aging-related synovial inflammation involves chronic recruitment of systemically derived immune cells that secrete cytokines and proteases[26] and is linked to the heightened systemic inflammation characteristic of aging and osteoarthritis[27]. As a reservoir of immune cells during disease, the synovium is further influenced by immunosenescence, which impairs immune cell function, leading to defective inflammatory resolution and dysregulated tissue catabolism[28], further shaping synovial crosstalk with cartilage and the surrounding joint tissues (fat, bone, meniscus, nervous system). The combined impaired immune cell functionality and capacity of resident synovial cells to clear infiltrating cells further promotes the chronic inflammatory phenotype of aged and osteoarthritic joints[23, 29]. The age-related shift in synovial signaling not only drives OA pathology but also alters the normal reparative responses of cartilage.

Fat and Synovium: Intra-articular fat depots and synovial tissue are key sources of inflammatory mediators that drive OA progression. Aging exacerbates adipocyte dysfunction and synovial inflammation, contributing to a pro-catabolic joint environment[3]. How aging-related changes in adipose tissue secretions (e.g., increased pro-inflammatory adipokines) influence synovial fibroblast activation and cytokine production remains unknown. Tools like proteomics and spatial transcriptomics to identify key signaling pathways as targeting these individual tissues is difficult given the presently available tools. Whether anti-inflammatory agents targeting adipokine signaling (e.g., leptin inhibitors) can reduce synovial inflammation and improve cartilage health is implicated across studies, but remains unknown.

Synovium and Bone: The synovium regulates nutrient and oxygen supply to joint tissues, including subchondral bone, and these tissues may be the first to demonstrate pathological signs of OA in spontaneous joint degradation[30]. Both are highly innervated and vascularized. Since aging leads to a pro-inflammatory synovial phenotype, which disrupts normal bone remodeling and contributes to OA-associated subchondral bone changes, it remains unclear how these changes can affect each other to drive OA. For example, considering the efficacy of anti-inflammatory or pro-angiogenic therapies in reducing synovial inflammation and restoring healthy bone remodeling in aged joints.

Meniscus and Cartilage: Aging impacts both cartilage and meniscus tissue integrity, leading to altered biomechanical properties, increased susceptibility to injury, and impaired repair mechanisms[31, 32]. The meniscus undergoes degenerative changes, including reduced collagen content, matrix remodeling, and cellular senescence, which disrupts its ability to support cartilage homeostasis. Similarly, cartilage degeneration exacerbates meniscal dysfunction, creating a feedback loop of tissue damage. Understanding the biochemical and biomechanical crosstalk between these tissues is essential for identifying therapeutic targets.

The nervous system and the joint: An overall decrease in sensory innervation of the knee joint has been observed with age, which precedes the development of age-associated cartilage damage in mice[33, 34]. Aging also is associated with the development of mechanical allodynia and hyperalgesia, indicative of sensitization of the nervous system[35-37]. By 2 years of age, signs of age-associated structural damage develop, and at this time point nerve sprouting has been observed in the subchondral bone and in the synovium, similar to findings in young post-traumatic OA mouse models[38] and in human TKA samples[39]. Finally, the cell bodies of the sensory nerves innervating the knee joint are housed in the dorsal root ganglia (DRG). Studies analyzing the DRG have shown increased numbers of macrophages and expression of chemokines and inflammatory mediators in aged vs young DRG[35] again similar to other work performed in young post-traumatic OA mouse models[11, 40-42].

Conclusion: Aging disrupts communication between joint tissues, contributing to OA progression through cellular senescence, inflammation, and reduced tissue repair. Standardizing research methods—such as biomarker profiling, animal models, imaging techniques, and co-culture systems—is crucial to ensure consistency, comparability, and the development of targeted interventions for OA in aging populations.

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