Q1. Are the mechanisms of aging-associated OA different from those of post-traumatic OA (PTOA)?

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Response/Recommendation: Yes. Age-associated OA and PTOA share fundamental pathological features; however, key mechanistic differences exist, particularly in the timing and magnitude of joint tissue remodeling, inflammatory responses, mitochondrial dysfunction, oxidative stress, and biomechanical drivers. Therefore, investigators should address their research question in both spontaneous and PTOA models to distinguish between shared and phenotype-specific OA processes and maximize therapeutic translational.

Strength of evidence: Moderate

Rationale: In spontaneous pre-clinical models of **age-associated OA**, joint pathology develops progressively with age across species[1]. In commonly used C57BL/6 mice, cartilage lesions, proteoglycan loss, subchondral bone plate sclerosis, and upregulation of catabolic enzymes and inflammatory mediators are evident by around 12 months and worsen progressively with age[2-5]. These age-related changes closely recapitulate the gradual progression of human OA rather than the acute and rapid pathology seen in injury-induced models. In age-associated OA, joint degeneration can affect joint tissues in both medial and lateral compartments[6], in contrast to PTOA models, where damage is typically focal and unilateral, localized to the site of trauma. Pain-related behavior emerges late, with older mice (20 months) showing increased mechanical allodynia and knee hyperalgesia when compared to younger mice (6 months), consistent with late-onset sensitization[4].

Osteoarthritis (OA) in younger adults usually occurs because of prior joint injuries, causing **PTOA**. Common PTOA models include destabilization of the medial meniscus (DMM)[7], anterior cruciate ligament transection (ACLT)[7], medial meniscectomy (partial/total)[8], intra-articular fracture (IAF)[9], as well as non-invasive models like mechanical ACL rupture or cyclical joint loading[10]. These models recapitulate PTOA and enable mechanistic studies and therapeutic testing across species. Chemical models like collagen-induced arthritis (CIA) and monoiodacetate (MIA)[11] can induce non-physiological bone erosion and inflammation, limiting their translational value[12,13]. In well-established surgery models of PTOA in mice, joint pathology develops rapidly following trauma/injury. In DMM-induced OA, cartilage degradation, proteoglycan and enhanced OARSI scores were higher than controls at 2 weeks and increased over the 10-week time course in mice[14]. Increased bone mineral density and subchondral bone sclerosis has been observed as early as 4-5 weeks post-surgery, reflecting rapid bone remodeling[14,15], coinciding with significant chondrocyte apoptosis[16]. Synovial hyperplasia and inflammatory cytokine production are detectable within 1-week post-surgery and are enhanced as OA progresses[15]. These models enable rapid assessment of joint degeneration and inflammation, offering a compressed timeline to study the structural and molecular features of OA. Pain-related behavior develops within weeks after joint injury, with mechanical hypersensitivity emerging at 8–12 weeks, continuing alongside joint degeneration[17].

Age-associated OA is closely linked to the hallmarks of aging[18,19] that drive progressive joint degeneration, whereas PTOA is initiated by acute injury/trauma. Accordingly, this review compares age- and PTOA-associated mechanisms that are supported by robust experimental evidence from preclinical animal models.

Cellular senescence and the senescence-associated secretory phenotype (SASP): In the context of **age-associated OA,** senescent cells accumulate in joint tissues (inc. chondrocytes, synovium, and bone) as an organism ages, an effect postulated to drive age-associated joint degeneration independent of injury[20,21]. These cells express $p16^{INK4a}$ in an age dependent manner and secrete a sustained SASP rich in pro-inflammatory cytokines, chemokines, growth factors and matrix-degrading enzymes that promote inflammation, suppress cartilage reparative processes, and drive extracellular matrix degradation[20-22]. Intra-articular transplantation of senescent fibroblasts in mice leads to cartilage erosion, osteophyte formation, and progressive loss of joint mobility, indicating that senescent cells are sufficient to remodel the joint microenvironment and drive OA like changes[23]. Genetic and pharmacologic clearance of senescent cells in aged mice reduces SASP and attenuates OA pathology, supporting a causal role for senescent cells driving age-associated OA rather than being a by-product of aging[24]. **In PTOA,** senescence and the SASP is rapidly induced as a direct consequence of surgery/injury and can be attenuated by selective elimination by senolytics[25]. This injury-induced senescence arises within days to weeks, much faster than the gradual accumulation observed in age-associated OA, acting early to drive joint degeneration rather than reflecting joint aging.

Inflammation: **In age-associated OA**, chronic and persistent low-grade systemic and local inflammation (termed inflammaging) has been shown to drive joint degeneration and is intricately related to enhanced oxidative stress,

senescence and the SASP. **PTOA** is characterized by rapid and transient inflammation**,** driven by acute joint injury-induced cytokine release that peaks early after trauma and diminishes over time[26,27]. Through meta-analysis and integrated multi-omics, Iijima et al[2] demonstrated that age-associated knee OA and post-traumatic OA (PTOA) are biologically distinct in mouse models of OA, with only 2.9% overlap in differentially expressed genes, indicating fundamentally different transcriptional and inflammatory programs. Age-related OA was shown to be driven by chronic, age-specific inflammation centered on impaired autophagy and robust AGE–RAGE signaling, not evidenced in PTOA. In the context of systemic inflammation, heterochronic parabiosis studies reveal that young systemic factors can partially reverse age-related musculoskeletal decline, whereas an aged systemic environment accelerates joint tissue degeneration[28,29]. In a non-invasive tibial compression mouse model[30], differentially expressed genes associated with inflammatory and immune pathways peaked at 1 day (599 genes) and 1 week (644 genes) post-surgery, and declined by 6–12 weeks (although some genes like MMP3 remained elevated at week 12), indicating an acute response despite ongoing cartilage damage. Similar PTOA models show early rises in pro-inflammatory mediators and immune cell markers within 3–14 days[27].

Mitochondrial dysfunction and oxidative stress: Mitochondrial dysfunction and oxidative stress are implicated in both age-associated and PTOA, but with distinct temporal and mechanistic features. In **age-associated OA** models, gradual declines in mitochondrial function, reduced mitochondrial biogenesis, and impaired antioxidant defenses, including decreased mitochondrial SOD2 and inhibition of Prx3, leads to oxidative stress levels of reactive oxygen species (ROS)[31-33] that are associated with an imbalance between anabolic (e.g. decreased IGF-1/AKT) and catabolic (e.g. enhanced MAPK) signaling events, and subsequent joint tissue degradation. Overexpression of Prx3 reduces the severity of age-related OA in old mice, supporting a role for mitochondrial ROS in age-related disease[31]. In contrast, **PTOA** models exhibit an acute increase in mitochondrial ROS and early suppression of antioxidant defenses, within days of injury, driving inflammatory and catabolic signaling that promotes OA[34,35]. In a rat model of PTOA, surgery caused gait impairment, oxidative stress, mitochondrial dysfunction, and increased apoptosis, effects that were all significantly reduced by intra-articular administration of the mitochondria-targeted antioxidant SkQ1[35]. Similar protective effects (using NAC or amobarbital) were also observed in a porcine IAF model[34]. Thus, while excessive ROS contribute to cartilage degeneration in both contexts through redox-sensitive signaling, age-associated OA reflects cumulative mitochondrial decline and sustained oxidative stress, whereas PTOA represents an injury-triggered acute oxidative insult.

Biomechanical instability and joint loading: In **age-associated OA**, chronic biomechanical alterations in cartilage and subchondral bone contribute to progressive joint degeneration. With age, articular cartilage accumulates AGE's, leading to collagen cross-linking, matrix stiffening, and reduced proteoglycan content that increases susceptibility to damage under normal loading, while age-related changes in subchondral bone remodeling contribute to altered load distribution and sclerosis[36]. By contrast, **PTOA** is initiated by acute joint destabilization/trauma that produces aberrant joint kinematics, elevated shear stress, and abnormal contact mechanics, rapidly driving cartilage matrix disruption, chondrocyte injury, meniscal ossification and osteophyte formation in animal models. Abnormal subchondral bone remodeling, including increased turnover, trabecular changes, sclerosis, and early osteophyte formation, develops within days to weeks after injury/trauma and further alters joint mechanics to accelerate cartilage degeneration[37]. Therefore, age-associated OA reflects chronic mechanical damage resulting from cumulative changes to joint tissues, whereas PTOA is driven by acute mechanical overload and instability, though both ultimately converge on joint degeneration.

Conclusion: Few studies have directly compared age-associated OA and PTOA under the same conditions. Comparative analyses using matched cohorts are required to define overlapping versus distinct mechanisms and accelerate the development of phenotype-specific therapies. Panx3 protects against age-associated OA but drives OA pathology after joint injury, demonstrating that the same molecular pathway can have opposing effects depending on context, highlighting the need to understand these mechanisms for targeted treatments[38,39]. Based on current literature, it is **recommended that animal models of age-associated and PTOA should be regarded as converging on similar clinical endpoints (joint dysfunction and degradation), while arising from fundamentally distinct initiating mechanisms and disease trajectories**. Critically, the processes that drive these OA phenotypes are not independent, but interconnected, whereby perturbations in one OA process can exacerbate others, ultimately leading to a degenerative joint microenvironment that drives OA progression. Although pathological changes across all joint tissues contribute to joint failure and OA, most mechanistic studies have focused on cartilage and chondrocytes. However, recent work has begun to examine the effect of age and injury on the subchondral bone[3,40,41], meniscus[42,43], ligaments[42,44], fat pad and synovium[45,46]. Continued investigation into age- and injury-associated mechanisms in all joint tissue/cells in both male and female animals will define the shared and specific processes involved and will likely lead to new therapeutic strategies for OA.

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