2026 ORS ICM on OA Models and Consensus Articles – Aging and OA Group (Q4)

Do all the hallmarks of aging play a role in aging-associated osteoarthritis (OA) development?

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Response / Recommendation

Yes. Across human, animal, and mechanistic studies, each of the 12 updated hallmarks of aging (genomic instability [1], telomere attrition [2,3], epigenetic alterations [4–6], loss of proteostasis [7], disabled macroautophagy [8,9], deregulated nutrient sensing [10–12], mitochondrial dysfunction [13–16], cellular senescence [17–19], stem-cell exhaustion [20,21], altered intercellular communication [22], chronic inflammation [23], and dysbiosis [24,25]) has supporting evidence linking it to OA initiation or progression [26,27].

Level of Evidence Moderate

Methodology

We performed a structured search (PubMed, Embase, Web of Science; through August 2025) using combinations of osteoarthritis with each hallmark (e.g., cellular senescence [17–19], mitochondrial dysfunction [13–16], autophagy [8,9], epigenetic alterations [4–6], telomere attrition [2,3], genomic instability [1], mTOR/AMPK/SIRT signaling [10–12], stem-cell exhaustion [20,21], SASP/exosomes [22], chronic inflammation/inflammaging [23], and dysbiosis/gut microbiome [24,25]). We prioritized recent systematic or narrative reviews, OARSI Year-in-Review articles [6], and mechanistic primary studies in human tissues or validated animal models. Study quality was assessed narratively; no meta-analysis was performed. The 2013 and 2023 Hallmarks of Aging frameworks were used to map evidence [26,27].

Findings by Hallmark

All hallmarks show some role; evidence strength is heterogeneous.
Strong: senescence [17–19]; mitochondrial dysfunction [13–16]; proteostasis/autophagy [7–9]; epigenetics [4–6]; altered communication [22]; chronic inflammation [23].
Moderate: nutrient sensing [10–12]; stem-cell exhaustion [20,21].
Emerging: genomic instability [1]; telomere attrition [2,3]; dysbiosis [24,25].

Cellular senescence — Strong. Senescent chondrocytes accumulate with age and OA severity; SASP factors drive matrix degradation and inflammation [17–19].

Mitochondrial dysfunction — Strong. OA cartilage exhibits impaired biogenesis and mitophagy with excess ROS; improving mitochondrial quality control mitigates OA features [13–16].

Loss of proteostasis / ER stress — Strong. Proteostasis collapse and ER stress promote apoptosis and catabolism in OA chondrocytes [7].

Disabled macroautophagy — Strong. Autophagy is reduced in aging and OA cartilage; restoration via AMPK–mTOR modulation is protective [8,9].

Epigenetic alterations — Strong. Reproducible DNA methylation, histone, and non-coding RNA changes regulate OA-relevant genes [4–6].

Altered intercellular communication — Strong. SASP factors and extracellular vesicles propagate catabolic signaling within joint tissues [22].

Chronic inflammation — Strong. Low-grade, chronic inflammation (inflammaging) accelerates OA progression [23].

Deregulated nutrient sensing — Moderate. Reduced AMPK and Sirtuin activity with increased mTOR signaling contributes to OA phenotypes [10–12].

Stem-cell exhaustion — Moderate. Aging mesenchymal progenitors show diminished reparative capacity; MSC trials show symptomatic benefit with variable structural outcomes [20,21].

Genomic instability — Emerging. DNA damage markers are increased in OA cartilage, though causal hierarchy remains unclear [1].

Telomere attrition — Emerging. Shortened telomeres and reduced telomerase activity are reported in OA chondrocytes [2,3].

Dysbiosis — Emerging. Gut microbiome alterations correlate with OA risk and severity; causal evidence is growing [24,25].

Recommendation

Adopt a hallmarks-guided framework for OA research and clinical trial design, incorporating biological stratification [26,27]. Prioritize senescence-, mitochondria-, and autophagy-targeted strategies in early-phase trials [7–19]. Integrate anti-inflammatory and epigenetic approaches with lifestyle interventions [4–6,23]. Investigate microbiome-informed adjunct therapies in mechanistically enriched OA subgroups [24,25].

Conclusion

OA is the prototypical aging-associated joint disease. The 12-hallmark framework illustrates how intracellular stress (genomic [1], epigenetic [4–6], proteostatic [7], mitochondrial [13–16]) and systemic cues (inflammaging [23], dysbiosis [24,25], altered intercellular communication [22]) converge on chondrocyte dysfunction, extracellular matrix degradation, and failed tissue repair. The most actionable hallmarks currently include senescence, mitochondrial dysfunction, impaired autophagy/proteostasis, and chronic inflammation, while others require stronger causal evidence.

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