2026 ICM -Aging and OA group

Question 11: Should we recapitulate in our animal models the genetic-epigenetic interactions at play systemically during aging and OA?

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RESPONSE/RECOMMENDATION: Yes, but it depends on the specific research question. Several complementary strategies can be considered to incorporate systemic genetic–epigenetic context into OA models, including but not limited to:

1. **Epigenetics:** Inducible Epigenetic Aging: Use models where epigenetic aging can be accelerated systemically (e.g. SAMP8 mice, ICE mice[1]) to test if an "older" epigenome lowers the threshold for mechanically induced OA.
2. **Metabolomics:** Since metabolism is a key driver of epigenetic modification (via SAMe and Acetyl-CoA availability), placing animals on a high-fat diet accelerates biological aging and creates a "systemic metabolic OA" phenotype (MetOA) that better recapitulates the human condition than surgical induction alone.
3. **Genetics:** Use of Diversity Outbred (DO) Mice: Instead of inbred strains, DO mice mimic human genetic diversity. Studying OA in these mice allows us to identify how specific genetic backgrounds protect against or sensitize to age-related epigenetic drift.

LEVEL OF EVIDENCE: Moderate (preclinical evidence based on small animal *in vivo* models)

DELEGATE VOTE:

RATIONALE: Osteoarthritis (OA) is the most common musculoskeletal disease and one of the most common diseases associated with aging[2]. Although great strides have been made in our understanding of OA pathogenesis, several fundamental questions persist. The present question of whether to recapitulate genetic/epigenetic interactions in our animal models touches on one of these questions directly: Is OA best understood as a failure of the joint organ *alone*, or as a disease in which *systemic* organismal aging and/or metabolic derangements modulate joint-specific vulnerabilities? Previously published studies suggest that OA has distinct local epigenetic associations that exist throughout the disease spectrum, particularly within cartilage and subchondral bone[3–6]. Epigenetic changes have also been identified in the commonly-used post-traumatic murine models of OA and in murine aging[7–9].

In human OA, genetic risk loci may establish a permissive or vulnerable state during development or early adulthood with age-related epigenetic drift progressively lowering the threshold at which mechanical or inflammatory stress leads to joint disease and failure[10,11]. In other words, epigenetic drift may act as a rheostat,

modulating the responsiveness of joint tissues to OA induction, set by the genetic environment, following environmental perturbations. For instance, an extracellular matrix (ECM) gene with minor genetic changes may lead to an ECM that is weakened only at a critical threshold reached in older age.

Additional evidence for the importance of genetic:epigenetic interactions can also be found in the metabolomic analyses, where recent studies indicate that metabolic challenges, specifically those induced by obesity and diabetes, trigger systemic epigenetic alterations as well as accelerated biological aging that extend to joint tissues including cartilage and synovium. These metabolic challenges initiate complex genetic-epigenetic catabolic cascades, which act in concert to accelerate the onset of OA, may drive progression, and exacerbate OA symptomatology[12–16]. These may work either independently or in concert with similar aging-associated changes[17].

Conversely, evidence also exists that joint tissue (specifically, cartilage) epigenetic aging may be distinct from extraarticular tissues. For example, a previous study[18] found specific accelerated biological/epigenetic aging within cartilage from human OA patients, whereas matched peripheral blood from these same patients did not demonstrate similar accelerated epigenetic aging. Additional large-scale human studies have not demonstrated accelerated epigenetic aging in peripheral blood samples of OA patients compared to controls[19], nor within specific OA patient endotypes (e.g. rapid radiographic or pain progressors)[20]. These findings suggest that epigenetic alterations in OA are strongly tissue-specific, shaped by local mechanical and metabolic stresses within the broader context of systemic aging.

Given this evidence, to effectively study the age-associated OA and, when indicated, recapitulate genetic and epigenetic mechanisms, the rodent strain chosen is crucial. The table presented below reviews the major points of commonly-used OA rodent models from a genetic/epigenetic context.

Strain	**OA phenotype**	**Systemic context**	**Key genetic-epigenetic features**	**Limitations**
C57BL6/J	Inducible	Metabolic susceptibility, prone to metS/obesity with HFD	Demonstrates standard age-related methylation drift. Excellent metabolic epigenetic phenomena.	Generally requires traumatic induction. Aged OA phenotype mild and late (18-24m), inconsistent primary OA.
STR/ort	Accelerated spontaneous, mostly male	Polygenic risk. High systemic oxidative stress.	Genetic loading likely creates a primed epigenetic landscape	Genetic risk only moderately similar to human-associated SNPs (*GLIS3, COMP,* potentially *MATN3*)
SAMP8	Accelerated spontaneous, senescence-associated	Inflammaging, rapid systemic senescence, oxidative stress	Recapitulates the epigenetic SASP phenotype, epigenetic changes in mitochondria driven by ROS	Places a strong emphasis on senescence, does not integrate genetic risk
ICE	Not yet tested	Accelerated epigenetic aging via induced DNA double strand breaks	Phenocopies aging *in vivo* principally by advancing epigenetic aging	OA/skeletal phenotypes not yet evaluated, only systemic ICE mice available.
Diversity outbred (DO)	Variable	High heterogeneity, each mouse is genetically unique	Allows evaluation of genetic + environmental interactions, may be more reflective of population-level responses to epigenetic stressors	Range of OA phenotypes not yet well characterized

CONCLUSION: Across these approaches, epigenetic mechanisms should be viewed primarily as integrators of genetic susceptibility and environmental exposure, modulating cellular responsiveness rather than acting as single, deterministic drivers of osteoarthritis.

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