Scientific Literature Review: Genomic and Epigenetic Insights into Mast Cell Activation, NADPH Oxidase Dysregulation, and Wharton's Jelly Mesenchymal Stem Cell Modulation in Osteoarthritis

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Background and Objectives

Osteoarthritis (OA) is now recognized as a chronic inflammatory and oxidative disease rather than a purely mechanical joint disorder. Two major molecular systems—**mast cell activation** and **NADPH oxidase (NOX) dysregulation**, particularly the NOX4 isoform—drive the inflammatory and oxidative cascades that lead to chondrocyte apoptosis and matrix degradation. Mast cells in the synovium release histamine, IL-1, and IL-6, triggering persistent inflammation, while NOX enzymes generate reactive oxygen species (ROS) that amplify cartilage injury.

Genomic and epigenetic studies reveal that polymorphisms and methylation patterns in oxidative and inflammatory genes shape individual susceptibility. Variants in *NOX4*, *IL1B*, and *IL6* enhance ROS and cytokine output, while hypermethylation of antioxidant genes such as *NFE2L2* and *SOD2* reduces redox resilience. This dual genomic-epigenetic vulnerability transforms OA into a redox-immune disorder.

The aim of this review is to integrate current literature on mast cell and NOX interactions, highlight genetic and epigenetic determinants of these mechanisms, and explore how targeted nutrigenomic strategies and Wharton's Jelly–derived mesenchymal stem cells (WJ-MSCs) can restore balance and improve regenerative outcomes.

Methods

A narrative review was performed using PubMed, Scopus, and Web of Science (2004–2025). Search terms included *mast cells*, *NADPH oxidase*, *NOX4*, *oxidative stress*, *epigenetics*, and *Wharton's Jelly mesenchymal stem cells*. Peer-reviewed papers from *eLife*, *Heliyon*, *Redox Biology*, *Antioxidants*, *Stem Cells Translational Medicine*, and *Frontiers in Molecular Biosciences* were analyzed. Only studies with mechanistic, genomic, or therapeutic relevance to OA or oxidative-inflammatory regulation were included. Data were synthesized into a translational model linking immune activation, oxidative signaling, and regenerative modulation.

Results

Mast Cell Activation:

Schneider et al. (*eLife*, 2019) demonstrated that mast cell–derived tryptase induces chondrocyte apoptosis, while Liu et al. (*Heliyon*, 2024) showed increased IL-1, IL-6, and histamine in OA synovial fluid, replicating mast cell activation syndrome (MCAS). Nigrovic et al. (*Arthritis Res Ther*, 2004) confirmed mast cells as independent initiators of synovial inflammation. Up to 30 % of MCAS patients suffer chronic arthralgia misdiagnosed as OA (*Ann Allergy Asthma Immunol*, 2021). Synovial biopsy data show mast cell infiltration in roughly 70 % of OA cases (*Stanford Medicine*, 2019).

NOX-Mediated Oxidative Stress:

NOX4 amplifies joint damage by overproducing ROS that activate p38-MAPK and induce TNF-α and IL-1β expression. Chen et al. (*Redox Biol*, 2023) demonstrated that NOX4 overexpression accelerates cartilage catabolism, while NOX inhibition prevents subchondral bone remodeling and cartilage loss (*Antioxidants*, 2022). *Front Mol Biosci* (2022) reported that NOX-driven oxidative stress accounts for over 50 % of unexplained inflammatory flares in knee pain syndromes.

Genomic and Epigenetic Factors:

Polymorphisms such as *NOX4 rs3017887* and *rs1836882* increase ROS generation, while *IL1B* and *IL6* promoter variants elevate cytokine output. Epigenetic silencing of *NFE2L2* and *SOD2* diminishes endogenous antioxidant capacity, predisposing to redox overload and cartilage degeneration.

Nutrigenomic and Lifestyle Modulation:

Micronutrients and diet modify these pathways. Vitamins C and E decrease NOX-derived ROS by up to 50 % (*Nutrients*, 2020). Quercetin inhibits NOX activity and stabilizes mast cells (*Redox Biol*, 2023). Zinc and copper optimize antioxidant enzyme function, while omega-3-rich Mediterranean diets reduce cytokine activation and improve post-MSC recovery (*Stem Cells Transl Med*, 2021). Weight control, regular exercise, and vitamin D sufficiency lower oxidative markers and enhance joint perfusion (*JAMA Netw Open*, 2021).

WJ-MSC Modulation:

Wharton's Jelly–derived MSCs secrete IL-10, TGF-β, and antioxidant enzymes that suppress inflammation and neutralize NOX-generated ROS. Zhang et al. (*J Pers Med*, 2024) found that antioxidant co-therapy with WJ-MSCs increased chondrocyte survival and reduced OA scores. Preconditioning with diet and antioxidants before MSC therapy improved cartilage repair and pain reduction by 40–80 %. WJ-MSCs thus act as immunomodulators and redox stabilizers within the joint microenvironment.

Conclusions

Mast cell activation and NOX dysregulation form an interconnected network driving chronic inflammation and oxidative stress in OA. Genetic and epigenetic variations in these systems define patient susceptibility and therapeutic response. Modulating these pathways through antioxidant supplementation, dietary correction, and lifestyle optimization can reduce inflammatory load and prepare the joint for regeneration.

Wharton's Jelly–derived MSCs integrate seamlessly into this redox-immune framework. Their secretome restores cytokine balance, enhances mitochondrial stability, and promotes matrix regeneration. When delivered in a preconditioned, low-oxidative environment, they achieve superior survival and tissue integration. This evidence redefines OA as a reversible biochemical imbalance rather than an irreversible degenerative process, opening the door to precision-based regenerative therapies that address both genetic predisposition and environmental triggers.

References

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Clinical Impact and Implications in Regenerative Medicine

The mast cell–NOX axis offers a translational blueprint for regenerative medicine. Correcting oxidative and inflammatory imbalances prior to stem cell therapy improves cell engraftment, mitochondrial performance, and paracrine signaling. Identifying *NOX4* and *IL1B* variants enables clinicians to personalize antioxidant or detoxification regimens before MSC application.