International Journal of General Medicine

Dovepress
Taylor & Francis Group

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PERSPECTIVES

Cigarette and Electronic Cigarette Exposure in Osteoarthritis: Immune Dysregulation and Inflammatory Signaling Pathways

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Abstract: Osteoarthritis (OA) was once seen mainly as a degenerative joint disease, but more studies now show that inflammation also has an important role in its development and progression. Smoking may be one factor in this process. Findings from population studies are still not fully consistent, but cigarette exposure is known to affect immune function and inflammatory signaling. This suggests that its role in OA may be more complex than a simple risk factor. At the same time, the fast growth of electronic cigarettes (EC) use has raised new concerns, because its effects on joint tissues are still not clear. In this Perspective, we discuss how cigarette and EC exposure may affect OA through several related pathways, including synovial macrophage activation, damage-associated molecular pattern (DAMP)-mediated signaling, NF-κB activation, inflammasome activation, Th17/Treg imbalance, and changes in microRNA expression. These changes may disturb the synovial-cartilage microenvironment, increase cytokine and chemokine production, and promote joint tissue damage. We also discuss current problems in this field, such as inconsistent epidemiological results, limited OA-specific mechanistic studies, and the lack of reliable models for EC exposure.

Keywords: osteoarthritis, cigarette smoking, electronic cigarette, synovitis, immune dysregulation, inflammasome, NF-κB, microRNA

Introduction

Osteoarthritis (OA) is a major cause of chronic pain and disability around the world, and it has become an increasing public health problem.[1] In 2020, about 595 million people worldwide were living with OA, and this number may rise to nearly 1 billion by 2050, mainly because of population aging and the growing rate of obesity.[2] OA does not only damage joint structure, but also greatly affects mobility, physical function, and quality of life, so it is now one of the most important chronic musculoskeletal diseases worldwide.[3,4]

OA was long seen mainly as a degenerative disorder caused by mechanical wear and tear.[5] But this view is now thought to be incomplete. More and more studies show that OA is a whole-joint disease with a clear immune-inflammatory component, and synovitis, innate immune activation, and abnormal tissue responses all take part in cartilage damage, symptom severity, and disease progression.[6–8] In particular, the synovium is no longer seen as a passive tissue. It is now considered an active immune site where resident and recruited immune cells help maintain a low-grade inflammatory environment that promotes joint damage.[9,10]

In this setting, cigarette smoking is a possible lifestyle factor in OA development, but its role is still not fully clear.[11] The epidemiological link between smoking and OA is still debated, and observational studies and genetic studies have shown inconsistent findings.[12] Even so, smoking is well known to strongly affect immune function.[13] Recent clinical studies show that cigarette exposure can change both innate and adaptive immune responses and may leave lasting effects on cytokine responses and immune regulation even after smoking cessation.[14,15] These findings support the idea that smoking is not only a lifestyle exposure, but also a factor that may affect synovial inflammation, immune-cell activation, and joint tissue degeneration in susceptible individuals.[15]

https://doi.org/10.2147/IJGM.S611519
Received: 24 March 2026
Accepted: 6 June 2026
Published: 11 June 2026

At the same time, the fast increase in electronic cigarette use has introduced another type of exposure. Although electronic cigarettes (ECs) are often described as a safer choice than combustible cigarettes, emerging evidence from non-joint systems suggests that EC aerosols can also cause oxidative stress, inflammatory signaling, and immune dysfunction.[16] But their specific effects on OA-related tissues and pathways are still not clear. In this Perspective, we discuss the current evidence on the smoking–OA association and examine how both conventional cigarette smoke and EC aerosol may contribute to OA through six interrelated immune-inflammatory pathways: exposure-specific effects, synovial macrophage activation, DAMP-mediated nuclear factor kappa-B (NF-κB) signaling, inflammasome activation, T helper cell 17 (Th17)/regulatory T cell (Treg) imbalance, and microRNA (miRNA) dysregulation. By integrating these mechanisms into a single conceptual framework, we aim to clarify the potential role of smoking-related exposures in shaping the synovial-cartilage microenvironment and to highlight key directions for future OA-specific mechanistic and translational research.

The Smoking-OA Association: Current Evidence, Paradoxes, and Unanswered Questions

The relationship between smoking and OA has remained controversial for more than three decades.[17] Initial studies, such as those from the Framingham cohort, suggested that smoking might reduce the risk of knee OA. This idea persisted, with a 2015 review concluding that the overall research generally supports a modest protective effect of smoking on radiographic knee and hip OA.[17,18] At the same time, that literature was already marked by substantial heterogeneity in joint site, outcome definition, and adjustment strategy, making the apparent inverse association difficult to interpret and biologically difficult to reconcile with the well-established pro-inflammatory effects of smoking.[19]

A major source of this paradox appears to lie in study design. In a 2011 meta-analysis, Hui et al concluded that the apparent protective effect of smoking was likely false, because the negative association was seen mainly in hospital-based case-control studies and in analyses where smoking was treated as a secondary covariate rather than the primary exposure.[20] Their subsequent meta-analysis in 2013 similarly found no compelling evidence that smoking reduced OA progression.[21] More recently, an individual participant data meta-analysis combining the OAI, MOST, and CHECK cohorts found no differences between current, former, and never smokers across six knee OA outcomes, including radiographic progression, symptomatic OA, and WOMAC-based symptom trajectories.[22] A parallel multicohort study of hip OA also found no clear association between smoking and the prevalence, incidence, or progression of radiographic or symptomatic hip OA over 4–5 years.[23]

Importantly, the weakening of the "protective effect" hypothesis has not been replaced by a single, universally consistent harmful estimate. Some population-based analyses now report a positive association between smoking and OA prevalence, while recent genetically informed studies increasingly support a deleterious causal role.[24] In a 2022 Mendelian randomization (MR) analysis, genetic liability to smoking initiation was associated with increased risks of overall, hip, and knee OA even after accounting for BMI.[25] A 2025 MR/meta-analysis likewise linked smoking initiation and lifetime smoking to greater OA risk.[26] However, these newer data still do not completely solve the problem, because OA is not a single uniform outcome. Different studies use different endpoints, such as prevalence, incidence, radiographic changes, MRI-detected cartilage loss, pain, symptomatic OA, or joint replacement, and these outcomes do not reflect the same biological process. In particular, total joint replacement may be influenced not only by disease biology, but also by access to medical care, coexisting diseases, and differences in treatment decisions. This may partly explain why some studies based on joint replacement have reported inverse associations.[23,27]

Taken together, current evidence no longer supports the simple idea that smoking protects against OA. A more likely explanation is that the effect of smoking may differ by joint site, disease phenotype, and level of exposure. At the same time, the results can be affected by BMI, collider bias, residual confounding, and misclassification of outcomes.[18,28]

Several important questions still remain:

1. Does smoking have a stronger effect on inflammatory or rapidly progressive OA phenotypes than on OA in general?

2. Are symptoms and structural progression driven by the same pathways?
3. How should current, former, cumulative, and passive smoking exposure be separated in analysis?
4. Do sex, obesity, metabolic dysfunction, or genetic background change this association?

For ECs, the uncertainty is even greater.[29] Direct evidence focused on OA is still very limited. Most current concerns come from the broader orthopedic and musculoskeletal literature, which suggests that EC exposure may not be biologically inert and may affect bone biology, wound healing, inflammation, and immune function; however, direct evidence in joint tissues remains very limited.

Mechanisms of Immune Dysregulation

As shown in Figure 1, cigarette and EC exposure may contribute to OA-relevant immune-inflammatory changes through several linked pathways rather than a single mechanism. OA is now seen as a whole-joint disease in which synovitis, innate immune activation, abnormal tissue responses, and mechanical stress work together to drive joint damage and symptoms.[5,30] In this setting, cigarette smoke may act as an immune modifier by causing oxidative stress, changing cytokine responses, and disrupting immune function, which can prolong inflammation beyond the lungs.[5,13,31] EC aerosols are different from cigarette smoke, but they may also cause oxidative injury, inflammation, and immune changes, though their OA-specific effects are still unclear. In the following sections, we focus on six related mechanisms:

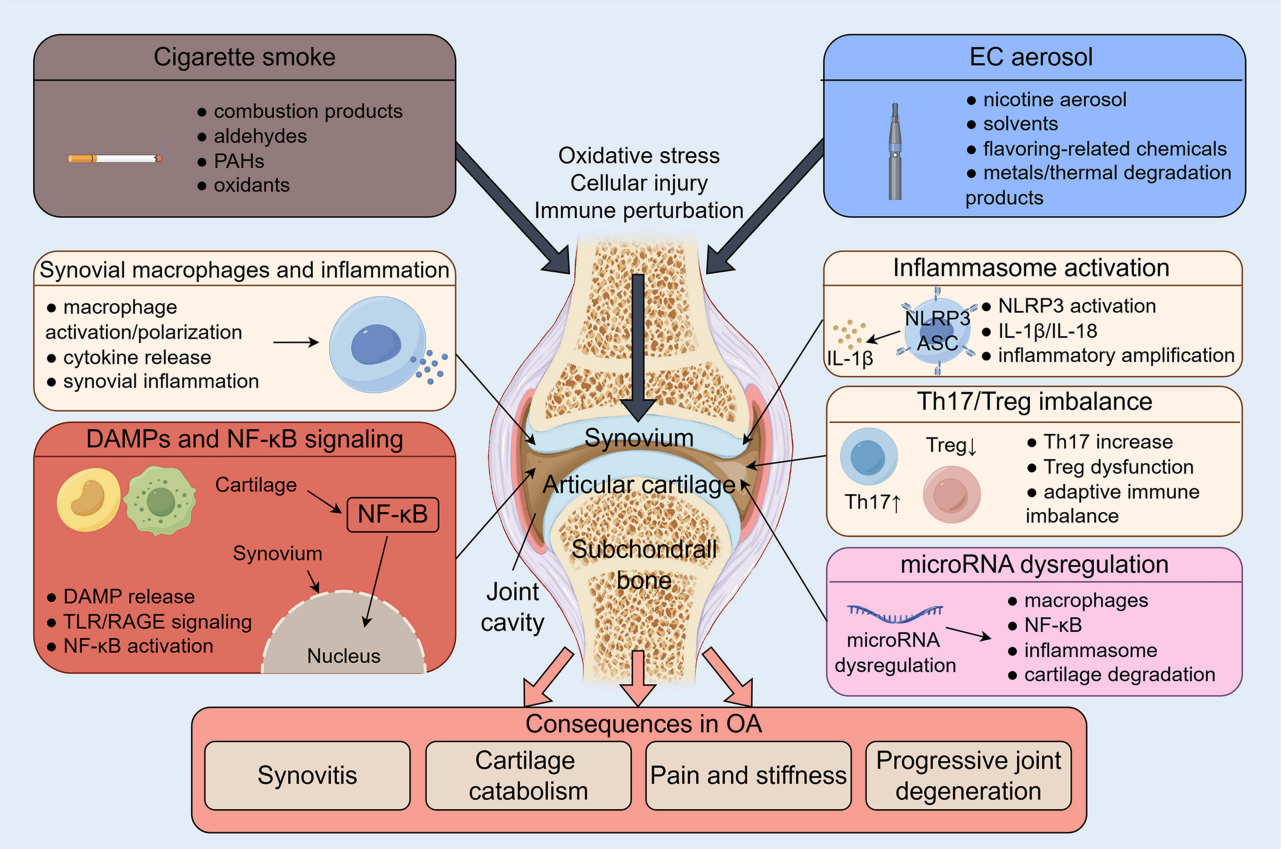

Figure 1 Proposed mechanisms by which cigarette and EC exposure drive immune dysregulation in osteoarthritis. Cigarette smoke and EC aerosol may act as immune-inflammatory modifiers in OA by perturbing the synovial-cartilage microenvironment. In this schematic, a central knee joint is used to illustrate how smoking-related exposures may promote local immune dysregulation and tissue injury. Although cigarette smoke and EC aerosol differ in chemical composition, both may induce oxidative stress, cellular injury, and inflammatory perturbation. These upstream effects may contribute to synovial macrophage activation, DAMP release and NF-κB signaling, inflammasome engagement, adaptive immune imbalance characterized by Th17/Treg disequilibrium, and miRNA dysregulation. Collectively, these pathways may enhance synovitis, amplify inflammatory mediator production, promote cartilage catabolism, and accelerate joint degeneration. EC-related mechanisms remain less well defined than those associated with combustible cigarettes, and some proposed links remain to be validated in OA-specific models. Upward arrows indicate increased activity/expression, whereas downward arrows indicate decreased activity/expression.

https://doi.org/10.2147/IJGM.S611519

exposure-specific effects, synovial macrophage activation, DAMP-mediated NF-κB signaling, inflammasome activation, Th17/Treg imbalance, and miRNA dysregulation. These pathways may contribute to synovitis, disturb synovium-cartilage crosstalk, and promote joint degeneration in susceptible individuals, although direct OA-specific evidence remains limited, particularly for EC exposure.[5,11]

Exposure Differences: Tobacco vs ECs

In OA research, conventional cigarette smoke and EC aerosol should not be viewed as the same type of exposure. Combustible cigarettes produce a complex mixture of toxic substances formed during combustion, including volatile aldehydes and polycyclic aromatic hydrocarbons (PAHs), which can be consistently detected in mainstream smoke under standardized smoking conditions.[32,33] By contrast, ECs produce heated aerosols rather than combustion smoke, and their chemical composition depends on several factors, such as e-liquid ingredients, nicotine type, flavor additives, device power, and puffing pattern.[34] Recent studies of nicotine salt-based electronic nicotine delivery systems (ENDS) have shown that EC aerosols can contain acetaldehyde, acrolein, and formaldehyde, while 97–99% of emitted particles fall within ultrafine or fine size ranges. Other mechanistic studies further suggest that PG/VG mixtures, flavoring compounds, and heating conditions can strongly affect aldehyde production.[34,35] These differences are important because they suggest that cigarette smoke and EC aerosol may trigger inflammation through partly shared, but not fully identical, upstream mechanisms.

This distinction also has biological importance. EC aerosol is unlikely to be immunologically inert. Experimental studies, largely from non-joint models, suggest that it may generate reactive oxygen species, induce oxidative stress-related cell death, activate NF-κB signaling, and increase IL-1β production and inflammatory cell infiltration.[36] In human nasal mucosa, both cigarette smoking and EC use have been shown to suppress the expression of immune-related genes. At the same time, EC users may show broader transcriptomic changes, including changes in cytokine and receptor signaling pathways. Long-term inhalation studies also indicate that EC exposure may disturb inflammatory and immune homeostasis.[37,38] Still, direct mechanistic evidence in OA remains limited.[39] Cigarette smoke extract has been reported to reduce viability, proliferation, and matrix formation in primary human chondrocytes, while EC vapour condensate impairs the viability and function of primary human osteoblasts.[40,41] Taken together, these findings suggest that tobacco and EC exposure should not be merged into a single category, although the OA-specific consequences of EC exposure remain to be established. In OA-related research, they should be studied separately, with careful attention to exposure chemistry, dose, and tissue-specific immune effects.

Synovial Macrophages and Inflammation

Synovial macrophages are important immune cells in OA because they can link systemic inflammation to local joint damage.[42,43] In the OA synovium, macrophages are not a uniform cell population. Under normal conditions, they help monitor tissue status and maintain local balance. But as OA progresses, some of these cells shift toward a more inflammatory and damaging state. Recent studies have repeatedly shown that synovial macrophages play a central part in OA-related synovitis, pain, and cartilage damage. This effect is partly due to their interaction with fibroblast-like synoviocytes, chondrocytes, and other infiltrating immune cells.[42,43] Although the M1/M2 model does not fully capture the diversity of macrophages in vivo, it is still useful for understanding their general roles. Macrophages with a more inflammatory phenotype usually increase cytokine release, oxidative stress, and matrix breakdown, while those with more reparative features are linked to inflammation control and tissue homeostasis.[44] Studies in experimental OA have also shown that changing synovial macrophage activation or polarization can reduce synovial inflammation and cartilage injury. This supports the view that synovial macrophages are active drivers of disease rather than passive bystanders.[45]

This macrophage-centered view is also important when considering cigarette and EC exposure.[46,47] In non-joint tissues, cigarette smoke has been shown to affect macrophage recruitment, phenotype, phagocytosis, efferocytosis, reactive oxygen species handling, and cytokine signaling, which suggests broad macrophage reprogramming rather than one simple polarization change.[46,47] Experimental and transcriptomic studies further show that smoke exposure can recruit monocyte-derived macrophages with pro-inflammatory and tissue-remodeling features. In some settings, nicotine or smoke-conditioned environments may also push macrophages toward dysfunctional immunosuppressive or M2-like

states.[48] In the same way, EC exposure can disturb innate immune balance, including macrophage phagocytic function, and long-term aerosol inhalation can change immune-cell transcriptional programs and inflammatory mediators in the lung.([38,49]) Although most of these findings come from pulmonary models, they still suggest that synovial macrophages may be an important link between cigarette or EC exposure and OA progression. Smoking-related macrophage reprogramming may increase synovitis, strengthen cytokine and chemokine signaling, and promote catabolic crosstalk with cartilage, which may lead to a more inflammatory OA phenotype.

DAMPs and NF-κB Signaling

One important way by which cigarette and EC exposure may affect OA is through cellular stress signals that trigger innate inflammatory responses in the joint.[50] In OA, tissue damage is not only a result of disease progression, but also a source of further inflammation. Stressed or injured joint cells, together with degraded extracellular matrix components, can release DAMPs, such as HMGB1, S100 proteins, advanced glycation-related ligands, and matrix fragments.[51,52] These endogenous danger signals are sensed by pattern-recognition pathways, especially TLRs and RAGE, and then promote inflammatory signaling in synovial and cartilage tissues. More and more OA studies support the idea that the DAMP–PRR axis links mechanical or metabolic injury with low-grade synovial inflammation, and this may explain how noninfectious tissue stress can maintain chronic immune activation even when no pathogens are present.[50]

In this setting, NF-κB is an important downstream signaling hub.[53] Activation of NF-κB in OA-related cells is associated with increased production of pro-inflammatory cytokines and chemokines, as well as matrix-degrading enzymes such as MMPs and ADAMTS. In this way, inflammation becomes closely linked to cartilage catabolism and structural joint damage.[53–55] Cigarette smoke is well known to cause oxidative stress and activate redox-sensitive inflammatory pathways, including NF-κB. Experimental studies also show that EC aerosols can induce oxidative injury, activate NF-κB, and trigger acute inflammatory responses.[36] Although direct evidence from OA-specific exposure models is still limited, it is biologically reasonable to think that smoking-related oxidative stress may increase DAMP release and strengthen DAMP–TLR/RAGE–NF-κB signaling in the synovial-cartilage unit. In this Perspective, we view this axis as an important mechanistic link between smoking-related exposure and the persistent inflammatory microenvironment that drives synovitis, cartilage damage, and OA progression.[56]

Inflammasomes in OA

Inflammasomes may be one of the links between smoking exposure and immune activation in OA. Among them, the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome has been studied the most in OA because it connects danger sensing with caspase-1 activation, IL-1β and IL-18 maturation, and pyroptosis-related inflammation.[57] Recent studies have emphasized the importance of NLRP3 in synovitis-related OA research. In a rat model of temporomandibular joint OA, NLRP3 expression was increased in synovial tissue, and inhibition of NLRP3 or caspase-1 reduced synovitis, pyroptosis, and IL-1β release.[57,58] In the same way, more and more OA studies link inflammasome activity with cartilage injury, synovial inflammation, and progression of whole-joint disease. This suggests that inflammasome signaling is not just a secondary downstream event, but may be an important pathogenic pathway and a possible therapeutic target.[59]

This framework is also useful for understanding cigarette and EC exposure, because both may share upstream triggers of inflammasome activation, such as oxidative stress and mitochondrial dysfunction. In cigarette smoke-related diseases, inflammasomes, especially NLRP3, have been implicated in several organs, although their effects may differ across tissues and may even appear inconsistent in some settings.[60,61] EC exposure may also affect inflammasome-related pathways. In a human study including nonsmokers, EC users, and cigarette smokers, circulating ASC, caspase-1, and IL-1β showed exposure-related changes that were consistent with altered inflammasome signaling.[62] However, direct evidence in OA-related tissues is still limited, and it remains unclear whether cigarette and EC exposure trigger the same inflammasome programs in synovium or cartilage. In this article, inflammasome signaling is viewed as a promising but still incompletely understood mechanism in smoking-related OA, linking stress sensing, macrophage activation, cytokine maturation, and joint inflammation.

Th17/Treg Imbalance and Joint Inflammation

Adaptive immune dysregulation, especially imbalance between Th17 and Treg cells, may also be involved in smoking-related OA. Recent studies show that OA patients often have higher Th17-related inflammation and weaker Treg-mediated regulation in synovial fluid and blood.[63] This change is important because Th17 cells promote IL-17-driven inflammation and tissue-destructive signaling, while Treg cells help limit excessive immune activation and maintain local immune tolerance.[63] In the OA joint, stronger Th17 activity may worsen synovitis, increase cytokine production, and further disturb the interaction between synovium and cartilage. The imbalance between Th17 and Treg cells may also help explain why some forms of OA appear more inflammatory and symptomatic than their structural damage alone would suggest.

This pathway is also relevant to cigarette and EC exposure because smoking has been increasingly linked to long-lasting changes in adaptive immunity.[15] Large human immune profiling studies show that smoking affects both innate and adaptive immune responses, and some adaptive immune changes can remain even after smoking cessation, which suggests a lasting immunological effect.[64] More specifically, smoking-related pro-inflammatory shifts in the Th17/Treg balance have been reported in chronic inflammatory conditions, including chronic pain and cigarette smoke exposure models, where increased Th17 bias or reduced Treg control has been observed.[65] These findings suggest that cigarette exposure, and possibly EC exposure, may worsen OA by strengthening both innate and adaptive immune responses. However, it is still unclear whether this mainly affects symptom severity, synovitis-dominant OA, or structural progression.

MicroRNAs as Biomarkers

MiRNAs are important in OA because they connect biological mechanism with measurable signals.[66] As post-transcriptional regulators, they can influence inflammatory signaling, matrix turnover, cell survival, and cell differentiation, all of which are closely related to synovitis and cartilage degeneration.[66] At the same time, miRNAs can be detected in blood, synovial fluid, exosomes, and joint tissues, which makes them promising biomarker candidates for disease classification and monitoring.[67] Recent studies on OA molecular biomarkers show that, despite clear progress in this field, there are still no clinically established molecular biomarkers for early OA diagnosis or for tracking disease progression, and this problem also applies to miRNA-based methods.[66,67] Therefore, miRNAs should not be seen as independent diagnostic markers, but rather as possible parts of multi-marker panels that may better reflect OA heterogeneity, including inflammatory phenotypes that may be more common in smoking-related disease.

This biomarker perspective is vital because smoking can alter systemic miRNA profiles related to inflammation and immune function.[68] In a large human study from the Framingham Heart Study, cigarette smoking was associated with a distinct six-miRNA signature, and several of these miRNAs were linked to C-reactive protein, interleukin-6, and immune-related gene networks; gain-of-function experiments further supported a role for smoking-associated miRNAs in inflammatory signaling.[68] More broadly, nicotine-related signaling has been linked to altered miRNA expression across multiple disease settings, supporting the idea that miRNA remodeling may represent one mechanism by which smoking leaves a persistent immunological imprint. For ECs, the field is even less mature.[69] Recent research suggests that miRNAs may help evaluate the health effects of vaping and may eventually distinguish EC-related biological responses from those of combustible cigarettes, but current evidence remains limited and far from OA-specific application.[67] These observations suggest that smoking-related miRNA dysregulation could play a key role in OA inflammation and serve as a biomarker for identifying OA subtypes linked to exposure in future research.

Challenges and Limitations

Research on smoking and OA still has several limits. First, epidemiological findings remain inconsistent, and some of this may come from study design rather than true biology.[22,23] Early reports suggesting a protective effect of smoking were influenced by hospital-based case-control studies and by analyses that did not focus on smoking as the main exposure.[70] Later studies did not support a protective role in OA incidence or progression, and recent individual-level analyses also failed to show protection in knee OA.[71] At the same time, OA itself is heterogeneous, and many studies

combine radiographic OA, symptomatic OA, pain, structural progression, and joint replacement, even though these outcomes do not reflect the same process.[72,73]

Second, direct mechanistic studies in OA-related tissues are still limited.[31] Some experimental work shows that cigarette smoke extract can worsen OA-like changes in cartilage explants and impair chondrocyte viability and matrix function.[40,74] The current mechanistic narrative largely relies on pulmonary, cardiovascular, or general inflammatory models instead of those specific to synovium, cartilage, or whole joints.[75,76] This is important because macrophages, inflammasomes, and adaptive immune pathways may act differently across tissues and exposure settings.[13,31]

Third, evidence for ECs is even less developed.[77] Reviews in orthopedics and general health suggest that EC exposure is not biologically harmless, but they also point out the lack of human clinical data, the small amount of orthopedic evidence, and uncertainty about long-term tissue effects.[29,77,78] In OA, this problem is larger because EC exposure varies widely by device type, nicotine formulation, flavor, power setting, and puffing pattern.[29,78] Therefore, studies that broadly describe "EC exposure" may actually be testing very different exposures.

Fourth, interpretation is made harder by the complex role of nicotine itself.[79,80] Nicotine is not always simply pro-inflammatory. In some settings it may show anti-inflammatory effects, while other components of cigarette smoke or EC aerosol may drive oxidative stress and inflammatory injury.[79,81] Thus, nicotine effects, cigarette smoke effects, and EC aerosol effects should not be treated as the same.[79,82,83] A similar problem exists in biomarker research. Although OA molecular profiling has advanced, there are still no validated biomarkers for early detection or progression monitoring, and this is even more difficult in smoking-related OA because biomarkers have not yet been clearly linked to exposure-defined OA subtypes.

These limits do not rule out a role for cigarette and EC exposure in OA through immune-inflammatory pathways. Instead, they show why the field remains fragmented: epidemiological findings are inconsistent, OA-specific mechanisms are not well studied, EC models are limited, and biomarkers are still immature.

Future Directions

Future studies should move from broad associations to OA-relevant models that can directly test smoking-related mechanisms.[31,82] Recent work shows that cigarette smoke extract can worsen cartilage degeneration and induce apoptosis, oxidative stress, mitochondrial dysfunction, and matrix abnormalities in OA chondrocytes, while TNF-α inhibition may partly reduce these effects.[13,40,82] This suggests that smoking-related damage is not only associative, but also mechanistically testable The next step is to build standardized models that study cigarette smoke and EC aerosol separately, with clear control of exposure chemistry, nicotine level, device setting, and dose. More useful systems may include synovium-cartilage co-culture, tissue explants, and whole-joint or organoid-like models, because they can better reflect immune-stromal interactions than single-cell systems.[5,82,84] This is especially important for EC research, since EC exposure may disturb both innate and adaptive immunity, while OA-specific models are still lacking.

Another priority is to define smoking-related OA at the cellular and spatial levels.[85] OA research is moving toward single-cell and spatial methods, and recent studies have started to map immune infiltration, signaling changes, and cellular remodeling in OA synovium and knee tissue.[85] These methods may help determine whether cigarette or EC exposure is linked to macrophage-rich inflammatory niches, altered fibroblast-immune interactions, or exposure-specific synovial programs that cannot be detected in bulk analysis.[5,40,86] Consequently, future studies should combine exposure history with single-cell transcriptomics, spatial transcriptomics, and immune phenotyping of synovial fluid and blood, so that hypotheses about macrophages, inflammasomes, and Th17/Treg imbalance can be tested directly in patient tissues rather than inferred from other organs.[87]

Biomarker research is also important. Although no OA biomarker class is ready for routine clinical use, biomarker-based stratification may still help early detection and precision trial design.[66,88] For smoking-related OA, future work should focus on exposure-specific biomarker panels rather than a single universal marker. These panels may combine smoking history, inflammatory mediators, miRNAs, imaging findings, and symptom patterns, with clear distinction between current, former, passive, and EC exposure.[26] These designs could clarify if smoking specifically affects inflammatory or rapidly progressing OA types instead of OA generally. Simultaneously, intervention studies should test if targets like NF-κB signaling, inflammasome activation, macrophage reprogramming, and TNF-related inflammation can identify subgroups that would benefit most from anti-inflammatory or exposure-reduction strategies. These research priorities are summarized in Figure 2.

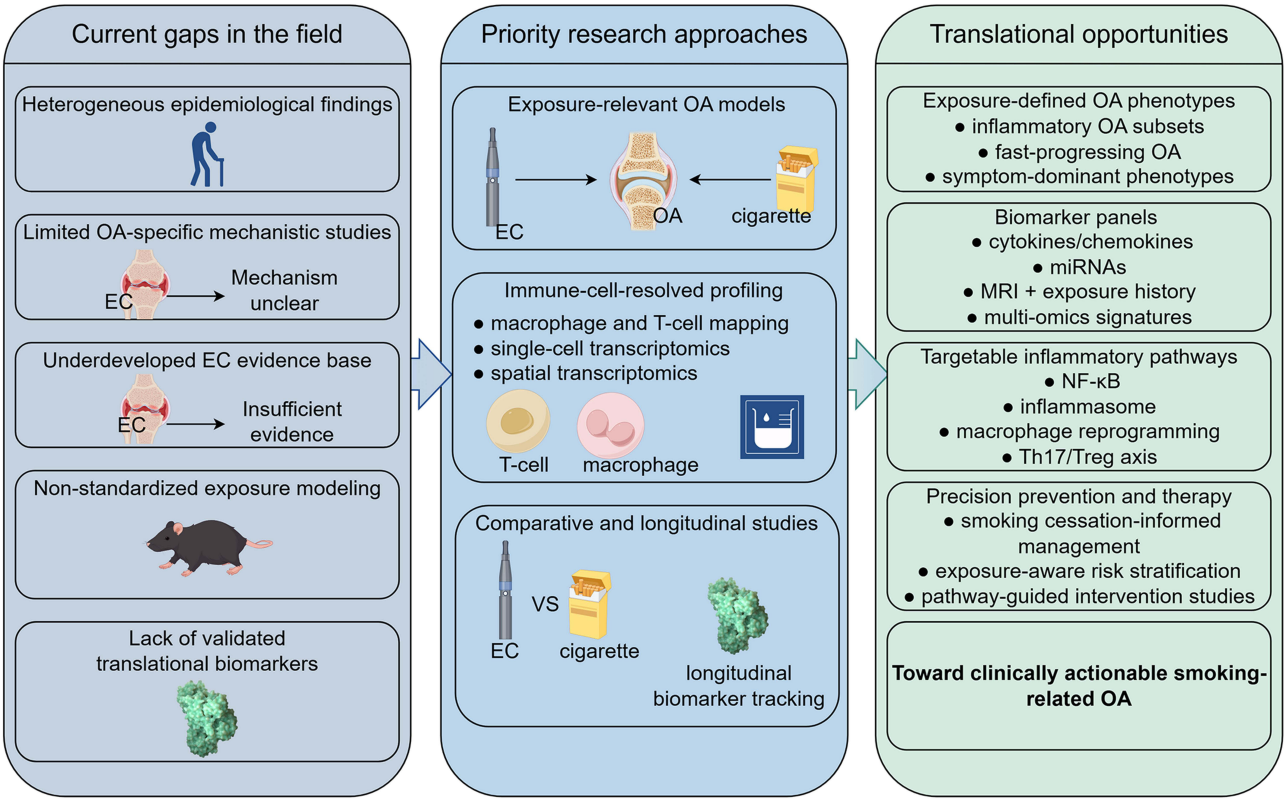

Figure 2 Research priorities and translational roadmap for smoking-related osteoarthritis. This schematic summarizes key future directions for research and translation in smoking-related OA. The left panel highlights major knowledge gaps that currently limit the field, including heterogeneous epidemiological findings, the scarcity of OA-specific mechanistic studies, underdeveloped evidence for EC exposure, non-standardized exposure modeling, and the lack of validated translational biomarkers. The central panel outlines priority research approaches needed to address these limitations, including exposure-relevant OA models that distinguish cigarette smoke from EC aerosol, immune-cell-resolved profiling using single-cell and spatial technologies, and comparative longitudinal studies integrating exposure history with OA phenotyping. The right panel illustrates potential translational outputs of this research framework, including exposure-defined OA phenotypes, biomarker panels, targetable inflammatory pathways, and precision prevention or therapeutic strategies. Collectively, these priorities may help reframe smoking-related OA as a biologically interpretable and clinically actionable subtype within the broader OA spectrum.

Conclusions and Perspective

Current evidence does not support the old view that smoking protects against OA. Instead, smoking is more likely to affect OA through changes in inflammation, immune responses, and tissue stress within the joint. This view fits better with the idea that OA is a whole-joint disease with an immune-inflammatory component. At present, the key issue is not simply whether smoking changes OA risk, but how cigarette and EC exposure may influence the synovial-cartilage microenvironment and potentially contribute to more inflammatory or fast-progressing OA phenotypes. Possible mechanisms include synovial macrophage activation, DAMP-mediated NF-κB signaling, inflammasome activation, Th17/Treg imbalance, and miRNA dysregulation. Compared with cigarette smoke, the effects of ECs on OA are still less clear and need more direct study. Overall, cigarette and EC exposure may be considered possible immune-inflammatory modifiers in OA rather than only background lifestyle factors, although the OA-specific effects of EC exposure require further direct investigation. This also supports the need for exposure-based OA phenotyping, separate mechanistic studies for cigarette smoke and EC aerosol, and further work on related biomarkers and inflammatory targets.

Generative AI Statement

The authors declare that no Generative AI was used in the creation of this manuscript.

Abbreviations

OA, osteoarthritis; DAMP, damage-associated molecular pattern; EC, electronic cigarette; miRNA, microRNA; NF-κB, nuclear factor kappa-B; Th17, T helper cell 17; Treg, regulatory T cell; MR, Mendelian randomization; PAHs, polycyclic aromatic hydrocarbons; OAI, osteoarthritis Initiative; MOST, multicenter osteoarthritis study; CHECK, cohort hip and cohort knee; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; BMI, body mass index; MRI, magnetic resonance imaging; PG/VG, propylene glycol/vegetable glycerin; IL, interleukin; PRR, pattern recognition receptor; HMGB1, high-mobility group box 1; TLR, Toll-like receptor; RAGE, receptor for advanced glycation end products; MMPs, matrix metalloproteinases; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; NLRP3, NOD-like receptor family pyrin domain containing 3; ASC, apoptosis-associated speck-like protein containing a CARD; TNF-α, tumor necrosis factor alpha.

Data Sharing Statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Acknowledgments

The Figure 1 (ID: ORIUW940a9) and Figure 2 (ID: AWTYA1a2aa) were created by Figdraw. All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure

The authors declare no conflicts of interest in this work.

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