Transcriptomic And Epigenetic Regulation of Menopause Associated Pain

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***Abstract*—Menopause, marked by oestrogen withdrawal, leads to a range of pain phenotypes, including musculoskeletal arthralgia, genitourinary syndrome, and fibromyalgia, driven by dysregulated gene expression across peripheral, spinal, and central tissues. This review explores the transcriptomic basis of menopause-associated pain, bringing together hormonal mechanisms such as TRPV1 upregulation, NF-κB-mediated neuroinflammation, and microRNA instability with advanced profiling approaches like RNA sequencing and single-cell analysis. It highlights tissue-specific expression patterns in the dorsal root ganglia, spinal cord, and blood, including sex-specific differences in pro-nociceptive genes such as SCN10A and Nav1.8, as well as epigenetic changes like DNA methylation and disrupted post-transcriptional regulation following oestrogen loss. Computational approaches, including differential gene expression analysis, functional enrichment, and network modelling using Cytoscape and miRNet, identify potential therapeutic targets such as NF-κB inhibitors, HDAC modulators, and miR-146a mimics. By addressing current gaps in menopause-specific, sex-stratified multi-omics data, this synthesis supports the development of precision therapies aimed at restoring regulatory balance, shifting pain management from symptomatic relief toward targeted, mechanism-based interventions to improve quality of life in menopausal women.**

***Index Terms*—Menopause-associated pain; Transcriptomics; Oestrogen withdrawal; Neuroinflammation; Genitourinary syndrome; Musculoskeletal pain; NF-κB signaling; MicroRNA regulation; RNA sequencing; Precision therapeutics**

I. INTRODUCTION

Menopause is a natural stage in every woman's life that marks the end of her reproductive years. It is confirmed when a woman has not had a period for 12 consecutive months, typically occurring between the ages of 45 and 55 [1]. Before this point, a transition phase called perimenopause begins, during which hormone levels gradually shift and menstrual cycles become irregular [2]. These changes occur because the ovaries progressively reduce their production of oestrogen and progesterone, eventually bringing menstrual cycles to a complete stop [3].

The fall in oestrogen causes a wide range of symptoms that affect most women to varying degrees, including hot flushes, night sweats, mood changes, sleep disturbance, and vaginal dryness [1]. Pain is an important but often overlooked part of this experience. Oestrogen plays a significant role in regulating how the body processes pain, and its decline during menopause can heighten pain sensitivity through both the nervous system and the musculoskeletal system [2]. This means that menopause does not simply mark the end of reproductive function; it fundamentally alters the biology of pain perception.

Understanding why menopause causes pain, and which genes and molecular pathways are responsible, is essential for developing better treatments. Transcriptomics — the large-scale study of which genes are switched on or off in cells — offers a powerful way to map these changes systematically [4]. This review examines transcriptomic approaches to menopause-associated pain with the aim of identifying molecular targets for more effective pain relief.

II. WHY UNDERSTANDING MENOPAUSE-ASSOCIATED PAIN MATTERS

Pain during menopause is far more prevalent and clinically significant than is often recognised. Musculoskeletal complaints alone affect over 70% of menopausal women, and genitourinary pain affects a substantial proportion of those in the postmenopausal

years [5, 6]. Unlike vasomotor symptoms such as hot flushes, which tend to ease over time, certain pain conditions, particularly genitourinary syndrome, are progressive without oestrogen treatment, meaning their burden accumulates rather than resolves [7]. Despite this, pain is often under-reported, under-diagnosed, and under-treated in this population, in part because its hormonal origins are not well understood by clinicians or patients alike.

Each woman's experience of pain during menopause varies. Hormonal changes do not fully explain this difference. Genetic factors, especially genes related to oestrogen signaling and metabolism, affect both when menopause starts and how severe the symptoms are [8, 9]. Studies spanning the genome have identified several genetic regions linked to menopause timing. This points to molecular mechanisms that we do not yet fully understand [8]. Such individual differences highlight the importance of investigating these mechanisms in detail instead of using a one-size-fits-all approach in clinics.

Transcriptomics allows researchers to study these mechanisms on a broad scale. By examining which genes are active in pain-related tissues at various stages of menopause, we can find the molecular markers that set apart women who experience significant pain from those who do not [4]. These findings have clear therapeutic benefits: gene expression patterns can highlight new drug targets, aid in the repurposing of current treatments, and support more tailored methods for managing menopause-related pain [10, 11].

Key Mechanisms of Menopause-Associated Pain

Musculoskeletal Pain

Musculoskeletal syndrome of menopause encompasses joint pain (arthralgia), loss of bone density, and accelerated cartilage deterioration [5]. These changes arise primarily from the loss of oestradiol, the most biologically active form of oestrogen, which plays a direct protective role in maintaining joint integrity and bone homeostasis [12]. As oestradiol levels fall, bone resorption outpaces formation, cartilage degrades more rapidly, and joint inflammation increases, producing the characteristic pain and stiffness of menopausal arthralgia.

A key problem with this presentation is the high rate of misdiagnosis. Menopausal arthralgia is often mistaken for inflammatory arthritis or osteoarthritis. This confusion can result in women getting unsuitable immunosuppressive treatments that don't tackle the hormonal cause. It's essential to distinguish between these conditions because menopausal arthralgia may respond to hormonal treatments that are usually not part of standard arthritis care. Identifying the gene expression patterns that differentiate menopausal musculoskeletal pain from inflammatory joint disease is an important opportunity for transcriptomic research.

Genitourinary Syndrome of Menopause

Genitourinary syndrome of menopause (GSM) describes the constellation of symptoms arising from oestrogen-deficient atrophy of the vaginal, vulvar, and urethral tissues [13]. As oestrogen levels decline, the urogenital epithelium thins and loses elasticity, and the local microbial environment shifts, producing a progressive symptom complex that includes vaginal dryness, burning, urinary urgency, dyspareunia, and increased susceptibility to infection [6]. These symptoms directly impair sexual function and quality of life yet remain significantly undertreated.

Unlike vasomotor symptoms, which frequently diminish over time, GSM is progressive in the absence of oestrogen replacement and does not resolve spontaneously [7]. The tissue changes underlying GSM are driven by the loss of oestrogen receptor signalling in urogenital epithelium, a process that has measurable consequences for local gene expression [14]. Transcriptomic profiling of urogenital tissues across menopausal stages therefore offers a direct window into the molecular drivers of GSM-associated pain and inflammation.

III. FIBROMYALGIA AND CENTRAL SENSITISATION

Fibromyalgia is characterised by widespread musculoskeletal pain, fatigue, and central sensitisation: a state in which the central nervous system amplifies pain signals beyond what peripheral injury alone would produce. Its prevalence and severity increase after menopause, and the association is particularly pronounced following surgical menopause via hysterectomy. This worsening is attributed to oestrogen loss disrupting the inhibitory pain pathways within the central nervous system that normally dampen pain signalling [15].

Because fibromyalgia is fundamentally a disorder of central pain processing rather than peripheral tissue damage, it is especially amenable to transcriptomic investigation of brain and spinal cord gene expression. The central sensitisation mechanisms that characterise fibromyalgia; including altered neurotransmitter signalling, glial cell activation, and dysregulated inflammatory gene expression; can be interrogated directly through RNA profiling of central nervous system tissues [16]. This makes fibromyalgia a particularly informative pain phenotype for understanding the broader transcriptomic consequences of menopause-associated oestrogen withdrawal.

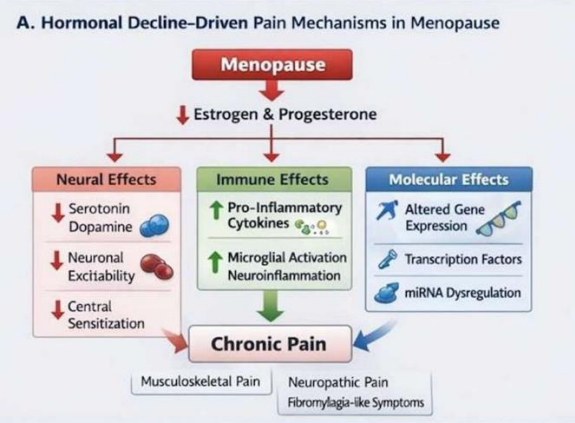

Figure 1: Hormonal Decline-Driven Pain Mechanisms in Menopause

Hormonal Changes and Pain Sensitisation Peripheral and Spinal Mechanisms

The shift toward heightened pain sensitivity at menopause reflects converging changes across multiple hormonal systems acting simultaneously at peripheral and spinal levels. Declining oestrogen impairs μ-opioid receptor function and allows upregulation of TRPV1, a key pain-sensing ion channel, on primary afferent nociceptors, together weakening descending inhibitory tone and lowering the threshold at which stimuli are perceived as painful [14,17]. These peripheral changes mean that ordinarily tolerable sensations are registered as noxious, even before any central amplification occurs.

Concurrently, progesterone withdrawal disinhibits spinal NMDA receptor activity, such that sub-threshold afferent input becomes sufficient to produce pain: the cellular mechanism underlying allodynia, in which innocuous stimuli such as light touch are experienced as painful [18]. Because peripheral sensitisation driven by TRPV1 upregulation feeds into a spinal cord already losing progesterone-mediated inhibition, each mechanism reinforces the other. The result is a pain processing system recalibrated toward greater sensitivity across multiple levels simultaneously, explaining the breadth and diversity of pain complaints that emerge at menopause.

Neuroinflammation and Central Pain Sensitisation

Beyond peripheral and spinal changes, oestrogen decline triggers a neuroinflammatory state that independently amplifies central pain processing. Oestrogen normally maintains microglia, the brain's resident immune cells, in a quiescent state through ERα-mediated suppression of pro-inflammatory gene transcription; its withdrawal permits microglial activation and the release of pro-inflammatory cytokines that elevate central inflammatory tone [19, 20]. This neuroinflammatory shift lowers pain thresholds centrally and sustains a state of heightened pain sensitivity that persists independently of ongoing peripheral input.

Oestrogen withdrawal additionally reduces brain-derived neurotrophic factor (BDNF), a neurotrophin that plays an integral role in descending pain suppression. Postmenopausal women show significantly lower BDNF levels than premenopausal controls, and hormone therapy has been shown to restore these levels toward premenopausal values [21] Menopause therefore does not merely lower the threshold at which pain begins; it simultaneously reduces the brain's capacity to suppress pain once initiated. Together, these central mechanisms help explain why menopausal pain can be so persistent and difficult to treat with conventional analgesics alone.

IV. TRANSCRIPTOMICS IN MENOPAUSE PAIN RESEARCH

Why Transcriptomics is Necessary

Pain arises from changes in gene expression across sensory neurons, spinal circuits, immune cells, and the brain. Transcriptomic profiling captures the complete set of active RNA transcripts in each tissue at a specific time. This provides a broad view of which biological processes are active, suppressed, or disrupted. [4]. This method goes beyond the limits of

candidate-gene studies, which can only test genes thought to be relevant. It can reveal molecular contributors that targeted methods might miss. [22].

During menopause, the withdrawal of oestrogen reorganizes gene expression across many systems related to pain. This level of coverage is not just helpful; it is essential. Oestrogen deprivation increases pro-inflammatory pathways, excitability genes like SCN10A/Nav1.8, and steroid metabolism networks. Hundreds of differentially expressed transcripts are found in perimenopausal cells without oestrogen. [23]. No candidate-gene approach could have captured the scale and coordination of these changes.

RNA Sequencing and DNA Microarrays

Two principal platforms are used for transcriptomic profiling, each suited to different research purposes. RNA sequencing (RNA-seq) provides unbiased, whole-genome coverage and can detect novel transcripts, splice variants, and non-coding RNAs without prior knowledge of what is expressed [22]. DNA microarrays measure hybridisation to pre-designed probes and are therefore limited to known sequences [24], though they remain cost-effective for large cohort studies [25]. In a direct comparison using a neuropathic pain model, RNA-seq identified a larger set of candidate genes and detected transcriptional changes in regions that microarray analysis missed entirely [26].

For menopausal pain research, RNA-seq is therefore the appropriate platform for discovery, while microarrays retain value for validation and biomarker studies in larger cohorts. This distinction was demonstrated by the successful use of microarrays to identify blood-based immune gene signatures that distinguished chronic pain patients from healthy controls [27]. The choice of platform should be determined by study purpose rather than technical preference, and ideally both approaches are used in sequence: RNA-seq for discovery, microarray for validation at scale.

Tissue Compartments: Peripheral, Central, and Blood

Transcriptomic studies of pain have been conducted across three principal tissue compartments, each offering a different and complementary perspective. The dorsal root ganglia (DRG), clusters of sensory neurons that relay pain signals from the body to the spinal cord, represent the most informative peripheral site. Spatial transcriptomics of human DRG has established that female nociceptor transcriptomes are constitutively distinct from male ones even at baseline [28], and this sex difference extends into disease states, where neuropathic pain patients show wholly non-overlapping differentially expressed gene sets between sexes [29,30]. These baseline differences are directly relevant to menopause, as declining oestrogen modifies a transcriptome already divergent from the male pattern.

Within the central nervous system, single-cell RNA sequencing of the spinal cord has revealed that pain chronification is accompanied by a male-specific inflammatory microglial subtype with no female equivalent, and that ApoE, the most upregulated gene in chronic-phase microglia, associates with chronic pain susceptibility in human genetic data [31]. Blood transcriptomics provides a non-invasive complement valuable for longitudinal study: sex-stratified analysis of circulating immune cells identified nearly twice the differentially expressed genes recovered by pooled analysis, including TCL1A, whose expression correlated directly with neuropathic pain severity and was validated at the protein level [27, 32]. Across all three compartments, sex-specific gene expression in pain is a consistent finding when study designs are built to detect it. This underscores the importance of sex-stratified study design, in which male and female data are analysed separately rather than pooled, as a methodological standard for transcriptomic pain research. Without this approach, the gene expression changes most relevant to menopausal pain risk being statistically diluted or missed entirely.

Transcriptomics Applied to Menopausal Pain

Applied directly to menopausal pain, transcriptomics enables comparison of gene expression in pain-relevant tissues — including DRG, spinal cord, joints, and blood — across premenopausal, perimenopausal, and postmenopausal stages. Oestrogen withdrawal has been shown to dysregulate genomic regulation broadly, upregulating pro-inflammatory cytokine pathways via NF-κB (a transcription factor), increasing expression of neuronal excitability genes, and altering steroid metabolism networks in ways that collectively lower pain thresholds [23]. These molecular shifts provide a mechanistic explanation for the clinical pain phenotypes observed across menopausal stages.

An important limitation of transcriptomics is that transcript levels do not perfectly predict protein abundance or function, meaning that differentially expressed genes require validation through proteomics or functional assays before causal claims can be made [4]. Despite this, the approach excels at nominating pain-relevant candidates and generating hypotheses for downstream investigation. Crucially, transcriptomic insights can directly prioritise therapeutic targets: genes consistently upregulated in postmenopausal pain states, such as oestrogen receptor modulators and inflammatory mediators, represent rational candidates for personalised pain relief strategies [10].

V. COMPUTATIONAL WORKFLOW FOR MENOPAUSAL PAIN TRANSCRIPTOMICS

Turning raw transcriptomic data into meaningful insights needs a structured analytical workflow with three steps: differential gene expression analysis, functional enrichment, and network analysis. Each step builds on the last, moving from statistical signals to biological insights relevant to menopausal pain.

Differential Gene Expression and Protein-Protein Interaction Mapping

Differential gene expression (DGE) analysis uses RNA-seq count data to identify genes whose transcription is statistically altered between conditions, for example between pre- and postmenopausal tissue. Tools such as DESeq2 and edgeR apply dispersion shrinkage, fold-change estimation, and multiple-testing correction to minimise false discoveries. Models must account for covariates including menopausal stage, age, and BMI, with low-count filtering and principal component analysis applied for quality control.

Table 1: Key Differentially Expressed Genes in Pain Pathways

Gene	Function	Role in Pain	Menopause Relevance
IL6	Cytokine	Inflammation	Increased post-estrogen decline
TNF	Cytokine	Pain signalling	Elevated inflammatory response
TRPV1	Ion channel	Pain perception	Sensory neuron sensitization
ESR1	Estrogen receptor	Hormonal regulation	Reduced signalling
NGF	Growth factor	Neuronal growth	Pain hypersensitivity

This process identifies genes whose expression is directly linked to oestrogen loss and pain sensitization. Meanwhile, protein-protein interaction (PPI) mapping using STRING places differentially expressed genes within known molecular networks. This shows connectivity patterns and highlights key genes. In pain research, this approach focuses on inflammatory mediators and SCN10A/Nav1.8, which become more excitable due to the loss of oestrogen.

Functional Enrichment Analysis

Once a list of differentially expressed genes has been established, functional enrichment analysis determines which biological pathways (KEGG, Reactome, Gene Ontology) are over-represented using GSEA or overrepresentation testing. Pain transcriptomes consistently highlight inflammatory pathways (cytokine signalling, MAPK cascades) alongside neural pathways governing synaptic transmission. In menopausal pain, neuroinflammatory enrichment reflects oestrogen loss driving microglial activation.

A key caution is that enriched pathways may reflect secondary responses rather than primary causal drivers, underscoring the need for multi-omics validation. Despite this, enrichment remains indispensable for converting long gene lists into interpretable biological themes.

Network Analysis

PPI networks visualised in Cytoscape identify hub genes (TLR4, SCN10A) representing regulatory leverage points. In the menopausal context, oestrogen loss reshapes inflammatory/nociceptive networks linking immune activation, matrix remodelling, and sensory neuron hypersensitivity. miRNet extends this by incorporating miRNA regulation (critical since oestrogen controls miRNA expression). This three-stage workflow provides a structured path from raw data to therapeutically prioritised menopausal pain targets.

VI. GENE REGULATORY MECHANISMS IN MENOPAUSAL PAIN

Transcriptional Regulation

Transcriptional regulation determines which pain-related genes are actively expressed through the binding of transcription factors to gene promoters. Oestrogen receptors (ERα and ERβ) act as ligand-activated transcription factors and can limit NF-κB–driven transcription of inflammatory mediators such as TNF-α and IL-1β in certain neural and immune contexts. With oestrogen withdrawal at menopause,

NF-κB–dependent inflammatory pathways become more active, promoting expression of inflammatory and nociceptive genes. [33]

Research has confirmed that menopause produces measurable shifts in transcription factor activity across pain-relevant tissues. Liu et al. identified distinct master transcription factor profiles characterising pre- and post-perimenopausal states in ovarian tissue, demonstrating that the hormonal transition fundamentally reconfigures transcriptional control [34]. Transcriptomic profiling of perimenopausal cells under oestrogen deprivation has further identified hundreds of differentially expressed transcripts enriched in NF-κB-dependent inflammatory pathways, confirming that oestrogen loss drives a coordinated shift toward pro-nociceptive gene expression [23].

Table 2: Regulatory Molecules in Menopausal Pain

Type	Molecule	Function	Pain Association
Transcription Factor	NF-κB	Inflammation control	Chronic pain
Transcription Factor	STAT3	Cytokine signalling	Neuropathic pain
miRNA	miR-21	Gene suppression	Inflammation
miRNA	miR-146a	Immune regulation	Neuroinflammation
miRNA	miR-155	Immune activation	Pain amplification

Epigenetics

Epigenetic modifications control gene expression without altering the DNA sequence. The two principal mechanisms are DNA methylation, where chemical tags silence transcription at gene promoters, and histone modification, where proteins packaging DNA are altered to loosen or tighten accessibility for transcription.

Aberrant DNA methylation across nociceptive gene promoters correlates with neuronal excitability in chronic pain. Persistent pain signaling alters DNA methyltransferase (DNMT) activity, such as DNMT3b downregulation in spinal nerve ligation models, leading to hypomethylation and upregulation of pain-related genes like GPR151 and CXCR3 [35]

VII. POST-TRANSCRIPTIONAL CONTROL OF PAIN-ASSOCIATED GENE EXPRESSION

Post-transcriptional control determines whether a gene that has been copied into messenger RNA is used to produce a protein, primarily through small molecules called microRNAs that bind to messenger RNAs and repress their translation (36). Because a single microRNA can regulate dozens to hundreds of targets, disruption to this system can broadly alter pain-related gene activity. Oestrogen directly regulates microRNA expression, meaning that its loss at menopause compromises this regulatory layer across pain pathways [37].

MicroRNAs that help reduce inflammatory signaling are often altered in pain conditions related to menopause. For instance, miR-146a, which typically limits NF-κB-dependent inflammation, is decreased in neuropathic pain models. Restoring its activity with miR-146a mimics helps ease pain by reducing upstream signaling molecules in the IRAK1/TRAF6 pathway. [38]. Disrupting the processes that create microRNAs in pain-sensing neurons, such as deleting key enzymes, leads to overactivity of pain-related genes and heightened pain responses. This highlights the critical role of this system in normal pain management. Therefore, restoring or adjusting microRNA activity offers a promising direction for treating menopause-related pain.

Integrated Regulatory Network

The transcriptional, epigenetic, and post-transcriptional mechanisms form an interconnected regulatory network rather than operating independently [14]. Oestrogen receptors act across these layers [37] so their loss at menopause disrupts gene control broadly: increased NF-κB activity drives inflammatory gene expression [19] promoting epigenetic remodelling at pain gene promoters [20] and sustaining pro-nociceptive states [40]. Transcriptomic studies of oestrogen-deprived perimenopausal cells have shown that these changes occur as coordinated shifts across many genes and pathways simultaneously, rather than as isolated events [23] Transcriptomics is uniquely positioned to capture disruption at this scale, making it the most appropriate tool for investigating menopause-associated pain at the systems level [4].

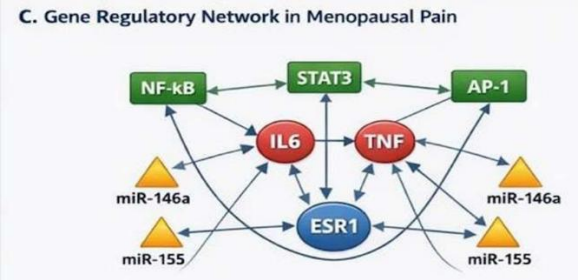

Figure 2: Gene Regulatory Network in Menopausal Pain

VIII. EMERGING MOLECULAR TARGETS FOR PAIN MANAGEMENT

The molecular mechanisms behind menopause-related pain reveal specific targets for treatment. TRPV1 is a pain-sensing ion channel that shows increased expression and activity when estrogen levels are low. It has been recognized as a target for treatment in several preclinical pain models. Both blockers that prevent TRPV1 activation and capsaicin-based agonists, which create long-lasting numbness in pain receptors, are currently being tested in clinical trials. [17, 41]Partially restoring the suppression of this pathway lost during menopause could significantly lower the transcription of inflammatory pain genes. [42]. DNMT inhibitors can reverse harmful methylation of pain-relief genes. Histone deacetylase (HDAC) inhibitors keep the chromatin structure open by stopping histone deacetylation, which promotes gene expression. These inhibitors have also proven effective in testing for pain management. [43].

MicroRNA-based approaches are likewise emerging as candidates for pain management. Restoring miR-146a activity, which suppresses NF-κB-driven inflammatory signalling, has shown promise in reducing neuropathic pain behaviours in preclinical models [38]. Gene-silencing technologies including siRNA and CRISPR-based approaches, which can selectively reduce expression of overactive pain-related ion channels such as TRPV1 and Nav1.8, are being explored as longer-term interventions in experimental systems [44]. While many of these strategies remain at the preclinical stage, they represent a shift toward targeting the specific molecular disruptions that menopause causes, rather than managing symptoms alone.

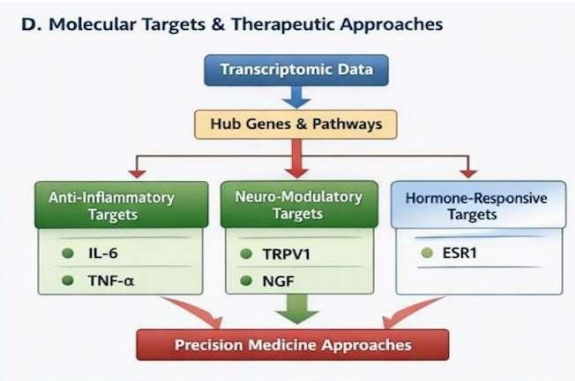

Figure 3: Molecular Targets & Therapeutic Approaches

IX. DISCUSSION

Menopause-associated pain reflects converging disruptions across multiple regulatory layers rather than a single hormonal change. Oestrogen loss disinhibits NF-κB-driven inflammatory transcription, promotes epigenetic silencing of analgesic genes, and destabilises microRNA control of nociceptive networks, producing overlapping musculoskeletal, genitourinary, and fibromyalgia phenotypes that share a common regulatory derangement.

A central challenge is that most transcriptomic pain research has not been conducted in menopausal populations and rarely includes sex-stratified analyses, so findings are extrapolated to menopausal women rather than derived from them, leaving tissue-specific signatures poorly defined and transcript-level changes largely unvalidated at the protein level.

Looking ahead, integrating transcriptomic, epigenomic, and proteomic data in sex-stratified designs offers a path to close these gaps. In parallel, single-cell RNA sequencing and multi-omics workflows that jointly profile genome, transcriptome, epigenome, and proteome at single-cell resolution can resolve the cell-type–specific regulatory programs obscured in bulk menopausal tissues. This enables identification of actionable nociceptive and immuno-inflammatory gene modules and, as these approaches scale to larger clinical cohorts, they will connect broad tissue pain signals to precise cell-level drug targets. [45]

X. CONCLUSION

Menopause-associated pain arises from a coordinated collapse of gene regulatory control driven by oestrogen loss, spanning transcriptional, epigenetic, and post-transcriptional mechanisms simultaneously. Transcriptomics offers the systems-level resolution necessary to characterise this complexity, and the molecular targets emerging from this approach, including NF-κB pathway components, epigenetic enzymes, and microRNA networks, represent a meaningful shift toward treatments that address underlying causes rather than surface symptoms. As sex-stratified research designs become standard and multi-omics integration matures, the prospect of personalised pain management for menopausal women moves from possibility toward clinical reality.

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