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Non-coding RNAs and epigenetic regulation in rotator cuff tendinopathy and tears

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Abstract

Rotator cuff tendinopathy and degenerative tears represent a leading cause of shoulder pain and disability and are associated with high failure rates after surgical repair. Emerging data have implicated non-coding RNAs, including microRNAs, long non-coding RNAs, and circular RNAs, together with epigenetic mechanisms such as DNA methylation and histone modifications, in the pathogenesis and healing potential of rotator cuff disorders. This narrative review synthesizes current evidence on these molecular regulators in human rotator cuff tissues and relevant experimental models, integrating their roles in inflammation, extracellular matrix remodelling, tenogenic differentiation, and muscle degeneration. It also explores their potential utility as biomarkers of disease severity and prognostic indicators of repair outcomes, and considers the feasibility of targeting non-coding RNAs and epigenetic pathways for regenerative therapeutics in shoulder surgery.

Keywords: *Rotator cuff tendinopathy, Non-coding RNAs, MicroRNAs, Circular RNAs, Epigenetics, DNA methylation, Histone modifications, Tendon healing, Tendon degeneration*

1. Introduction

Rotator cuff tendinopathy and degenerative tears are among the most frequent causes of shoulder pain, functional loss, and work disability in adults and older individuals. They arise through a combination of extrinsic mechanical factors and intrinsic biological processes, including chronic overload, hypovascularity, inflammation, and progressive extracellular matrix degradation. Despite advances in imaging and arthroscopic repair techniques, re tear rates remain substantial and many patients experience persistent symptoms or poor functional recovery, which has driven interest in deeper molecular characterization of rotator cuff pathology (Gumina *et al.*, 2023; Tashjian *et al.*, 2020; Thankam *et al.*, 2019).

Traditional studies focused on histological and biomechanical features and on single candidate genes and proteins. More recently, high throughput approaches such as RNA sequencing and epigenomic profiling

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have revealed complex gene expression changes and chromatin alterations in supraspinatus tendon and associated tissues. In parallel, non coding RNAs (ncRNAs), including microRNAs (miRNAs), long non coding RNAs (lncRNAs), and circular RNAs (circRNAs), have emerged as central post transcriptional regulators in musculoskeletal biology and tendon injury. These ncRNAs, together with DNA methylation and histone modifications, form an interconnected regulatory network that shapes cell fate, matrix remodelling, and inflammatory responses in rotator cuff tendinopathy and tears (Liu *et al.*, 2021; Ge *et al.*, 2020; Lyu *et al.*, 2023; Orchard *et al.*, 2023).

A rotator cuff specific narrative review has already synthesized miRNA expression changes in cuff tendon injuries and highlighted their diagnostic and therapeutic potential. Separate reviews have considered epigenetic mechanisms in tendon inflammation and healing more broadly. A recent systematic review has started to compile epigenetic alterations, including ncRNAs, in rotator cuff tendinopathy and degenerative cuff tears. However, a detailed, integrative synthesis focusing on the full spectrum of ncRNAs alongside classical epigenetic mechanisms in rotator cuff pathology has not been available. This narrative review therefore aimed to collate and interpret existing evidence on miRNAs, lncRNAs, circRNAs, DNA methylation, and histone modifications in rotator cuff tendinopathy and tears. It further examined their potential as biomarkers and therapeutic targets in regenerative shoulder surgery (Hatzinger *et al.*, 2025; Papalia *et al.*, 2023).

2. Methods

2.1. Design and rationale

This work used a structured narrative review design to synthesize mechanistic and translational evidence on non coding RNAs and epigenetic regulation in rotator cuff tendinopathy and degenerative tears. A narrative approach was chosen because the available literature was heterogeneous in methods, tissues, and outcomes and because the main aim was conceptual integration and critique rather than quantitative meta analysis (Sukhera, 2022a; Sukhera, 2022b).

2.2. Information sources and search strategy

Relevant studies were identified through electronic searches of PubMed/MEDLINE, Embase, Web of Science, and Scopus up to July 2026. Search terms combined rotator cuff and supraspinatus tendon descriptors with tendinopathy or tears, together with non coding RNA and epigenetic keywords. Examples of free text terms included “rotator cuff”, “supraspinatus tendon”, “tendinopathy”, “tear”, “microRNA”, “miRNA”, “long non coding RNA”, “lncRNA”, “circular RNA”, “circRNA”, “noncoding RNA”, “DNA methylation”, “histone modification”, and “epigenetic”. Where appropriate, MeSH or Emtree terms for rotator cuff, tendinopathy, microRNAs, and epigenetics were added. Reference lists of key primary studies and existing reviews on miRNAs, tendon epigenetics, and rotator cuff epigenetic alterations were screened to identify additional relevant articles (Hatzinger *et al.*, 2025; Thankam *et al.*, 2019).

2.3. Eligibility criteria and study selection

Studies were considered eligible if they met the following criteria: they investigated patients with rotator cuff tendinopathy or tears, or experimental models of rotator cuff tendon injury; they examined expression or function of non coding RNAs (miRNAs, lncRNAs, circRNAs) or epigenetic mechanisms (DNA methylation, histone modifications, chromatin state); and they reported molecular findings related to rotator cuff tissues or closely associated structures such as supraspinatus tendon, long head of biceps tendon, subacromial bursa, or adjacent muscle. Both human observational studies and experimental studies in animal models or tendon derived cells were included when they provided mechanistic insight into rotator cuff pathology or healing (Zhang *et al.*, 2022; Leal *et al.*, 2017).

Reviews, editorials, and conference abstracts were not included as primary sources of data but were consulted to contextualize the findings and to ensure that this narrative synthesis complemented existing work rather than duplicating it. Studies that focused exclusively on other tendons without clear rotator cuff relevance or that lacked ncRNA or epigenetic outcomes were excluded. Study selection proceeded iteratively, with titles, abstracts, and full texts screened for relevance to the integrative molecular question. Data extraction focused

on tissue type, pathology, ncRNA or epigenetic markers studied, analytical methods, principal findings, and any reported clinical correlations.

Because this was a narrative rather than systematic review, no formal PRISMA flow diagram or risk of bias assessment was undertaken. Instead, emphasis was placed on capturing key mechanistic and translational studies across ncRNA and epigenetic domains and on critically appraising their coherence, limitations, and implications.

3. Results

3.1. MicroRNAs in rotator cuff tendinopathy and tears

3.1.1. Expression patterns and signatures

Multiple studies reported distinct miRNA expression patterns in rotator cuff tendinopathy and degenerative tears. An explorative case-control study profiled circulating miRNAs in patients with chronic rotator cuff tendinopathy and degenerative rotator cuff tears compared with individuals without shoulder pathology. It identified several miRNAs with progressive deregulation across these groups, suggesting a continuum of molecular change from tendinopathy to full thickness tear. Serum signatures were partially mirrored by tendon biopsy samples, which showed similar repression of selected miRNAs in supraspinatus tendon tissue from patients with tears (Plachel *et al.*, 2020).

Another study examined miRNAs associated with inflammation in shoulder tendinopathy and glenohumeral arthritis and identified a set of miRNAs predicted to regulate inflammatory pathways, including cytokine signalling, matrix metalloproteinases, and immune cell activation, in rotator cuff injury and arthritis. These miRNAs were mapped to target genes involved in extracellular matrix homeostasis and inflammatory cascades, reinforcing the concept that miRNA dysregulation contributed to local tendon inflammation (Thankam *et al.*, 2019).

A narrative review focused specifically on microRNA expression changes in rotator cuff tendon injuries synthesized eleven studies and concluded that several miRNAs were key regulators of muscle architecture, fatty infiltration, fibrosis, and extracellular matrix synthesis in the presence of rotator cuff tears. The review highlighted miRNAs involved in myogenesis, adipogenesis, and fibrogenic pathways, and emphasized their potential as diagnostic biomarkers and therapeutic targets.

3.1.2. Functional roles and mechanistic studies

Beyond expression profiling, experimental work began to uncover functional roles for specific miRNAs in tendon disease. A Nature Communications study investigated miR 29a in tendon disease and showed that interleukin 33 induced tendon damage and regulated miR 29a, which in turn controlled collagen III production and fed back on IL 33 signalling in tendon tissue. The authors demonstrated that modulation of miR 29a altered collagen composition and tissue remodelling, suggesting that miR 29a played a central role in the balance between repair and fibrosis in tendon disease (Millar *et al.*, 2015).

In rotator cuff tenocytes, inhibition of miR 205 was shown to promote proliferation, migration, and fibrosis via regulation of the methyl CpG binding protein MECP2. This study implicated the miR 205/MECP2 pathway in tenocyte behaviour and matrix changes in rotator cuff tendinopathy, linking a specific miRNA to epigenetic regulation of gene expression. These mechanistic findings supported the broader notion that miRNAs influenced rotator cuff pathology not only through post transcriptional repression of target mRNAs but also through modulation of epigenetic regulators (Xiuhua and Zhenchun, 2022).

3.1.3. Clinical correlations and biomarker potential

Several studies examined associations between miRNA expression and clinical features of rotator cuff disease. The case–control miRNA profiling study reported that deregulated circulating miRNAs correlated with degenerative rotator cuff pathology and suggested that such signatures might serve as novel diagnostic or prognostic biomarkers for shoulder disorders. The rotator cuff specific miRNA review noted that particular miRNAs were associated with muscle fatty degeneration, atrophy, and tear size, consolidating the idea that miRNA panels could help stratify patients by disease severity and perhaps predict healing potential.

Although most studies were exploratory and involved small cohorts, the collective evidence indicated that miRNAs provided an additional level of regulation over traditional protein coding genes and could be harnessed as biomarkers or therapeutic agents once their roles were better validated.

3.2. Long non coding RNAs and circular RNAs in rotator cuff pathology

3.2.1. lncRNA expression and function

Long non coding RNAs emerged as another class of regulators in rotator cuff disease. A study that performed conjoint analysis of lncRNA and mRNA expression in rotator cuff tendinopathy compared supraspinatus tendon from patients with tendinopathy to normal tendon and used RNA sequencing to profile differentially expressed lncRNAs and mRNAs. The authors identified lncRNAs associated with inflammation, extracellular matrix organisation, and cell proliferation, and constructed co expression networks suggesting that specific lncRNAs modulated gene expression programmes relevant to tendon degeneration.

Experimental work in animal models provided functional evidence. One study investigated lncRNA H19 in a rat model of rotator cuff tear and in tendon derived stem cells from Achilles tendon. Overexpression of H19 accelerated tenogenic differentiation by modulating the miR 140 5p/VEGFA signalling axis and was associated with improved tendon healing. The findings supported a role for H19 as a positive regulator of tenogenesis and tendon repair and illustrated how lncRNAs could act through miRNA sponging and downstream growth factor pathways (Liu *et al.*, 2021).

More recently, research explored lncRNA CRNDE in tendon derived stem cells and rotator cuff injury repair. This study reported that CRNDE regulated differentiation of tendon derived stem cells and enhanced rotator cuff injury repair by modulating the miR 337/TGFBR2 axis. It proposed that CRNDE promoted tenogenic differentiation and matrix deposition via this pathway, further reinforcing the concept that lncRNAs controlled stem cell fate and tendon regeneration.

3.2.2. circRNAs and integrated ncRNA modules

Circular RNAs also contributed to rotator cuff pathology. A systems level analysis systematically identified aberrant non coding RNAs and their mediated modules in rotator cuff tears. Using RNA sequencing and network analysis, the authors profiled lncRNAs, miRNAs, and circRNAs in rotator cuff tendon tissue and constructed ceRNA networks that linked ncRNAs to mRNAs and pathways involved in inflammation, extracellular matrix and cell apoptosis. They found that specific circRNAs acted as miRNA sponges and participated in regulatory modules that might drive degenerative changes in rotator cuff tendon.

These data, although still limited in number, suggested that circRNAs added another layer of complexity to ncRNA mediated regulation in rotator cuff disorders and that integrated analysis of miRNAs, lncRNAs, and circRNAs was necessary to understand the full regulatory landscape.

3.3. Epigenetic mechanisms in rotator cuff tendinopathy and tears

3.3.1. DNA methylation and regulation of metalloproteinases

Epigenetic mechanisms, defined as heritable changes in gene expression that did not involve alterations in DNA sequence, played an important role in tendon biology and pathology. A study focusing on epigenetic regulation of metalloproteinases and their inhibitors in rotator cuff tears examined promoter methylation and expression of Matrix Metalloproteinases (MMPs) and Tissue Inhibitors of Metalloproteinases (TIMPs) in supraspinatus tendon tissue. It reported altered methylation patterns associated with differential expression of MMPs and TIMPs, suggesting that DNA methylation contributed to dysregulated matrix turnover and might influence tendon degeneration and healing.

This work provided a direct link between epigenetic marks and key effector molecules in rotator cuff pathology and implied that methylation changes could be targeted or monitored to modulate tissue remodelling.

3.3.2. Histone modifications and chromatin state

Histone modifications constituted another major epigenetic mechanism. A study on histone modifications in late stage rotator cuff tendinopathy used chromatin immunoprecipitation sequencing to assess trimethylation

of histone H3 at lysines 4 and 27 (H3K4me3 and H3K27me3). It found differences in the trimethylation status of these marks in diseased supraspinatus tendon compared with control tissue, with associated enrichment of genes involved in inflammation, matrix remodelling, and signalling pathways. These changes suggested that the chromatin landscape in late stage rotator cuff tendinopathy was altered in ways that could stabilise pathological gene expression patterns.

Broader reviews of epigenetic regulation in tendon healing described how DNA methylation, histone deacetylation, and histone modifications influenced tendon inflammation, fibrogenesis, and repair across various tendons, including rotator cuff, Achilles, and patellar tendons. These reviews argued that epigenetic mechanisms integrated biological and mechanical cues and contributed to chronic tendon degeneration.

3.3.3. Epigenetic synthesis in rotator cuff disorders

A recent systematic review on epigenetic alterations in rotator cuff tendinopathy and degenerative cuff tears compiled evidence from studies of DNA methylation, histone modifications, and ncRNAs in human rotator cuff tissues. It concluded that epigenetic regulation played an important role in the pathophysiology of rotator cuff tendinopathy and degenerative tears and that epigenetic alterations were likely to interact with mechanical and environmental factors to drive disease progression. This systematic synthesis provided a broader framework within which the specific findings on MMP/TIMP methylation and histone trimethylation could be interpreted.

3.4. Integrated non coding RNA–epigenetic regulatory networks

Emerging evidence indicated that non coding RNAs and epigenetic mechanisms formed interconnected regulatory networks in rotator cuff pathology. The study on miR 205 and MECP2 described how a miRNA could regulate an epigenetic factor, thus linking post transcriptional control to DNA methylation and chromatin state in tenocytes. The lncRNA studies demonstrated that lncRNAs such as H19 and CRNDE interacted with miRNAs and growth factor signalling to govern tenogenic differentiation and tendon healing, representing bidirectional crosstalk between ncRNAs and transcriptional regulation (Xiuhua and Zhenchun, 2022; Liu *et al.*, 2021).

The systems level analysis of aberrant ncRNAs and their mediated modules in rotator cuff tears showed that miRNAs, lncRNAs, and circRNAs formed co expression and ceRNA networks that converged on target mRNAs and pathways related to inflammation, extracellular matrix organisation, and apoptosis. When considered together with data on DNA methylation and histone modifications, these networks suggested that ncRNAs could either respond to or influence epigenetic marks and that the combined ncRNA–epigenetic architecture determined the phenotype of rotator cuff tendinopathy and tears.

Although direct experimental evidence of ncRNA control over specific epigenetic enzymes in rotator cuff tissue remained limited, analogous findings from other tendon and musculoskeletal tissues, as summarised by reviews on tendon epigenetics and sports related injuries, supported the plausibility of such interactions. Thus, a conceptual model emerged wherein mechanical stress, inflammation, and injury induced changes in ncRNA expression and epigenetic marks, which together reprogrammed tenocytes, tendon derived stem cells, and adjacent muscle fibres towards degenerative or reparative trajectories.

3.5. Biomarker and therapeutic implications

The accumulated findings had several potential clinical implications. First, deregulated circulating and tissue miRNAs in rotator cuff tendinopathy and tears appeared suitable for exploration as diagnostic and prognostic biomarkers. Studies showed that particular miRNAs were associated with disease presence and severity, muscle fatty infiltration, and fibrosis, and a dedicated review argued that miRNA panels could help classify rotator cuff disorders and predict outcomes. Integrated ncRNA modules involving lncRNAs and circRNAs might also yield biomarker candidates once validated.

Second, epigenetic marks such as DNA methylation patterns in MMP and TIMP promoters and histone trimethylation profiles in diseased tendon offered possibilities for tissue based biomarker development. The systematic review on rotator cuff epigenetic alterations underscored that such marks reflected chronic molecular changes that could inform prognosis or response to therapy.

Third, the mechanistic studies suggested potential therapeutic targets. Modulating miRNAs like miR 29a or miR 205 or lncRNAs such as H19 and CRNDE could, in principle, alter collagen composition, fibrogenesis, and tenogenic differentiation, thereby improving tendon repair. Reviews on miRNAs in tendon injury and tissue engineering discussed approaches such as miRNA mimics, inhibitors, and miRNA functionalised scaffolds as strategies to achieve sustained and local ncRNA delivery to tendon tissue. Epigenetic regulators, including DNA methyltransferases and histone modifiers, might be targeted with small molecule inhibitors or activators, although data specific to rotator cuff remained sparse.

Finally, ncRNA and epigenetic insights could inform the design of cell free biologics such as exosomes. Studies in tendon and rotator cuff injury showed that stem cell derived exosomes carried ncRNAs and proteins that influenced matrix remodelling and tenogenic differentiation, and there was interest in engineering exosomes to deliver specific miRNAs or lncRNAs to diseased tendon. Integrating ncRNA and epigenetic knowledge with such regenerative strategies could enhance the efficacy of biologic augmentation in shoulder surgery (Zou *et al.*, 2023; Connor *et al.*, 2019).

4. Discussion

This narrative review demonstrated that non coding RNAs and epigenetic mechanisms collectively contributed to the molecular landscape of rotator cuff tendinopathy and degenerative tears. MiRNA studies identified distinctive expression patterns in blood and tendon tissue and linked these to inflammation, muscle atrophy, fatty infiltration, fibrosis, and extracellular matrix synthesis. lncRNA and circRNA analyses revealed additional regulatory layers controlling tenogenic differentiation, stem cell behaviour, and gene networks relevant to tendon degeneration. Epigenetic investigations highlighted the roles of DNA methylation and histone modifications in regulating key matrix related genes and in establishing chromatin states characteristic of late stage rotator cuff tendinopathy.

The integrative picture supported a model in which mechanical overload, aging, metabolic comorbidities, and inflammatory stimuli triggered ncRNA and epigenetic reprogramming in rotator cuff tissues. These molecular changes then governed whether tenocytes and tendon derived stem cells adopted degenerative or reparative phenotypes and whether extracellular matrix and muscle architecture deteriorated or recovered. Although many findings were still preliminary and based on small cohorts or animal models, the convergence of data across multiple ncRNA classes and epigenetic marks strengthened the overall signal.

This narrative synthesis had limitations. It did not aim to exhaustively capture every study on ncRNAs or epigenetics in rotator cuff and tended to emphasise mechanistic and translational work that illustrated key pathways and regulatory modules. Risk of bias and study quality were considered qualitatively rather than through formal scoring systems. Furthermore, much of the evidence remained associative. Only a subset of studies included gain or loss of function experiments in relevant cells or animal models, and clinical trials of ncRNA or epigenetic targeted therapies in rotator cuff disease were lacking.

Another limitation was the relative scarcity of data on circRNAs and direct interactions between ncRNAs and specific epigenetic enzymes in human rotator cuff tissue. Most concepts regarding ncRNA–epigenetic crosstalk were extrapolated from broader tendon or musculoskeletal literature. As such, the integrated regulatory network proposed here should be treated as a working model that requires further experimental validation.

Despite these constraints, the review had several strengths. It used a structured approach to identify and organise studies across ncRNA and epigenetic domains and integrated them around clinically meaningful processes such as inflammation, extracellular matrix remodelling, muscle degeneration, and tendon healing. It also explicitly positioned its findings in relation to existing miRNA specific and epigenetic tendon reviews and to the recent systematic review of epigenetic alterations in rotator cuff tendinopathy and degenerative tears, thereby clarifying where this narrative synthesis added conceptual depth.

Future research should prioritise larger human cohorts with well phenotyped rotator cuff pathology and longitudinal sampling to determine whether ncRNA and epigenetic profiles predict repair outcomes or re tear risk. Multi omics approaches combining transcriptomics, epigenomics, proteomics, and imaging could refine molecular classifications of rotator cuff disease and identify actionable targets. Interventional studies

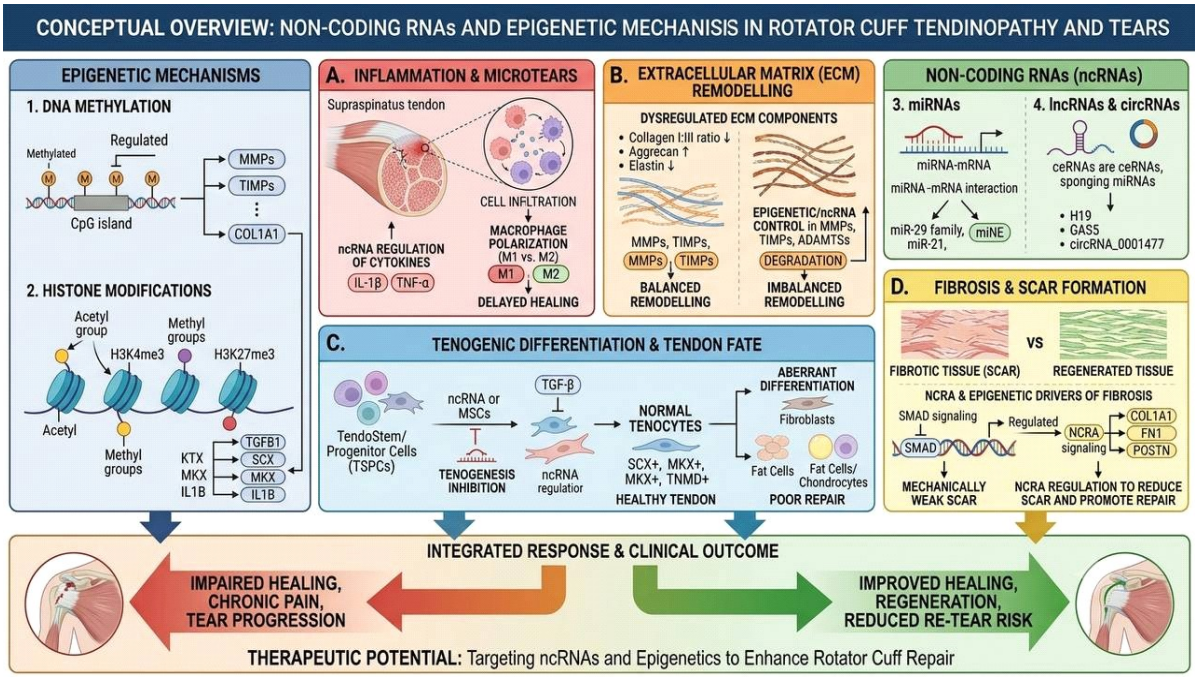

Figure 1: Conceptual overview of how non-coding RNAs and epigenetic mechanisms influence rotator cuff tendinopathy and tears, including inflammation, extracellular matrix remodelling, tenogenic differentiation, fibrosis, and healing response

Table 1: Representative non-coding RNAs discussed in rotator cuff pathology and their reported roles

ncRNA class	Example	Reported role	Citation no.
miRNA	miR-29a	Regulates tendon remodelling and collagen balance	23
miRNA	miR-205	Affects tenocyte proliferation, migration, and fibrosis via MECP2	24
lncRNA	H19	Promotes tenogenic differentiation via miR-140-5p/VEGFA	25
lncRNA	CRNDE	Enhances tendon-derived stem-cell differentiation and repair	26
circRNA	Multiple circRNAs	Participate in ceRNA modules linked to inflammation and ECM regulation	19,27

Table 2: Key epigenetic mechanisms in rotator cuff tendinopathy and tears and their putative functional implications

Mechanism	Target/process	Implication	Citation no.
DNA methylation	MMP/TIMP promoters	May alter matrix turnover and tendon degeneration	20
Histone modification	H3K4me3/H3K27me3 patterns	Associated with chronic pathological gene expression	10,28
ncRNA-epigenetic crosstalk	MECP2 and regulatory networks	Links post-transcriptional and chromatin-level regulation	24

that modulate specific ncRNAs or epigenetic marks in animal models and, eventually, in patients would be necessary to translate these molecular insights into therapies. There is also a need to understand how systemic factors, such as diabetes and aging, modulate ncRNA and epigenetic landscapes in rotator cuff tissue, given their known associations with tendinopathy and tear progression (Yuan *et al.*, 2024d; Liu *et al.*, 2021).

5. Conclusion

In summary, non coding RNAs and epigenetic mechanisms formed a complex regulatory network in rotator cuff tendinopathy and degenerative tears. MiRNAs, lncRNAs, and circRNAs, together with DNA methylation and histone modifications, influenced inflammation, matrix remodelling, tenogenic differentiation, and muscle degeneration in supraspinatus tendon and related tissues. These molecular regulators showed promise as biomarkers and potential therapeutic targets, although more robust mechanistic and clinical data were required. Integrating ncRNA and epigenetic knowledge with emerging regenerative strategies, such as biologic augmentation and exosome based therapies, could enhance outcomes of rotator cuff repair and may, in time, contribute to more personalized approaches to shoulder surgery.

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