Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2024.342537.3723 Volume 31, Issue 2, FEB. 2025, Supplement Issue
Manuscript ZUMJ-2412-3723
DOI: 10.21608/ZUMJ.2024.342537.3723
REVIEW ARTICLE

Long Non-Coding RNA Hox Transcript Antisense Intergenic RNA (HOTAIR) Possible Roles in Rheumatoid Arthritis

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Submit Date 07-12-2024
Revise Date 17-12-2024
Accept Date 19-12-2024

ABSTRACT

Background: Hox Transcript Antisense Intergenic RNA (HOTAIR), a well-studied Long Non-Coding RNA (lncRNA), is known to regulate gene expression through epigenetic mechanisms, primarily by interacting with Polycomb Repressive Complex 2 (PRC2) to modify histone methylation patterns. HOTAIR can modulate the expression of inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin (IL)-6, directly exacerbating the inflammatory environment within the joint. Its effects on synovial fibroblasts, crucial cells in rheumatoid arthritis (RA)-induced joint damage, are also being investigated. HOTAIR may influence fibroblast proliferation and the production of matrix metalloproteinases (MMPs), contributing to cartilage and bone erosion.The precise mechanisms through which HOTAIR exerts its effects in RA remain an area of active research. However, the consistent observation of its dysregulation in RA patients, coupled with its established roles in epigenetic modification and immune cell regulation, strongly suggests its potential as a therapeutic target and biomarker for RA. Future research focusing on specific HOTAIR-mediated pathways could lead to the development of novel therapeutic interventions to combat this debilitating disease. We aimed to present a summary of the role of lncRNA, HOTAIR, in RA patients.

Conclusions: HOTAIR's involvement in RA pathogenesis is multifaceted and involves interactions with numerous molecules and pathways. Further research is needed to clarify its precise mechanisms of action and the specific genes it regulates in RA, as well as exploring the complex interplay with other non-coding RNAs and signaling cascades. This research is critical for understanding the complexity of RA and for developing new therapeutic strategies that target HOTAIR or its interacting partners.

Keywords: Hox Transcript Antisense Intergenic RNA; Long Non-Coding RNA; Rheumatoid Arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by persistent inflammation of the synovial joints. Affecting approximately 1% of the global population, RA's prevalence shows some geographic variation. The disease is marked by debilitating symptoms, including joint pain, swelling, stiffness, and limited range of motion, often leading to significant functional impairment and reduced quality of life. Pathogenetically, RA involves a complex interplay of genetic predisposition and environmental triggers, initiating a cascade of immune dysregulation. The hallmark of RA is synovitis, the inflammation of the synovial membrane lining the joints. This inflammation is driven by immune cells, particularly T cells and B cells, which infiltrate the synovium, releasing pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, and IL-6. These cytokines stimulate the proliferation of synovial cells, leading to the destruction of cartilage and bone, ultimately resulting in joint damage and deformity. The autoimmune nature of RA is evidenced by the

presence of autoantibodies, such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), which target self-antigens within the joint [1].

Beyond the well-established roles of proteins and coding genes, the field of genomics has revealed a vast landscape of non-coding RNAs (ncRNAs), which exert significant regulatory functions in diverse cellular processes. A substantial portion of these ncRNAs are long non-coding RNAs (lncRNAs), defined as transcripts exceeding 200 nucleotides in length that lack significant protein-coding potential. LncRNAs have emerged as crucial players in the intricate choreography of gene expression regulation and cellular function. Their mechanisms of action are diverse and multifaceted. Some lncRNAs act as epigenetic regulators, interacting with chromatin-modifying complexes like Polycomb Repressive Complex 2 (PRC2) to influence histone modifications and alter gene expression. Others act as molecular scaffolds, bringing together different proteins to facilitate protein-protein interactions and downstream signaling events. Still others may act as decoys, sequestering regulatory proteins or microRNAs and modulating their activities. This complex interplay allows lncRNAs to participate in a wide array of cellular functions, including development, differentiation, and response to stress [2].

In general, lncRNAs are defined as non-protein-coding transcripts larger than 200 nucleotides. They are mainly transcribed by RNA polymerase II. Transcribed lncRNAs are further subjected to post-transcriptional processing, involving capping, polyadenylation, alternative splicing, and RNA editing. Sequence comparison across species has suggested a relatively low degree of evolutionary conservation of lncRNA sequences. Compared with mRNAs, lncRNAs are generally less stable, shorter, and have fewer exons. Most lncRNAs have fewer introns, with an average of one intron per lncRNA versus seven introns per protein-coding RNA. It was revealed that the nucleus is highly enriched with lncRNA. Some lncRNAs are located only in the cytoplasm and others in both the nucleus and cytoplasm. Three mitochondrial lncRNAs have been identified in the human genome that regulate three mitochondrial genes. LncRNAs are the most abundant ncRNA species in the mammalian genome. The biological functions of most lncRNAs are poorly understood. The first lncRNAs, H19 and X-inactive specific transcript (Xist), were discovered in the early 1990s. Since then, thousands of lncRNAs have been identified [3].

Long non-coding RNAs (lncRNAs) and the adaptive immune system

LncRNAs are involved in the regulation of adaptive immune responses. Lymphocytes (T- and B-cells) are the primary cellular mediators of the adaptive immune system. There is now clear evidence that lymphocytes express a large number of lncRNAs that play crucial roles in their development, differentiation, and activation. Many lncRNAs are involved in the regulation of the development and differentiation of various subsets of T lymphocytes. In addition, lincRNA clusters have been identified in T cell samples, from early T cell progenitors to terminally differentiated T cell subsets [4]. B cells, mediators of the antibody-dependent humoral arm of the adaptive immunity, also express lncRNAs. Very little is known about the regulation of lncRNAs of adaptive immune responses in normal B cells. FAS antisense transcript 1 lncRNA (Fas-AS1 lncRNA) tightly controls the production of soluble Fas receptor, which binds Fas ligand to regulate Fas-induced apoptosis in B-cell lymphomas. Since serum soluble Fas receptor levels are associated with poor prognosis in non-Hodgkin's lymphoma, the Fas-AS1 lncRNA is a potential therapeutic target in this setting. Whether lncRNAs also play a role in the maturation and the effector function of B-cells remains an open question (Figure 1) [5].

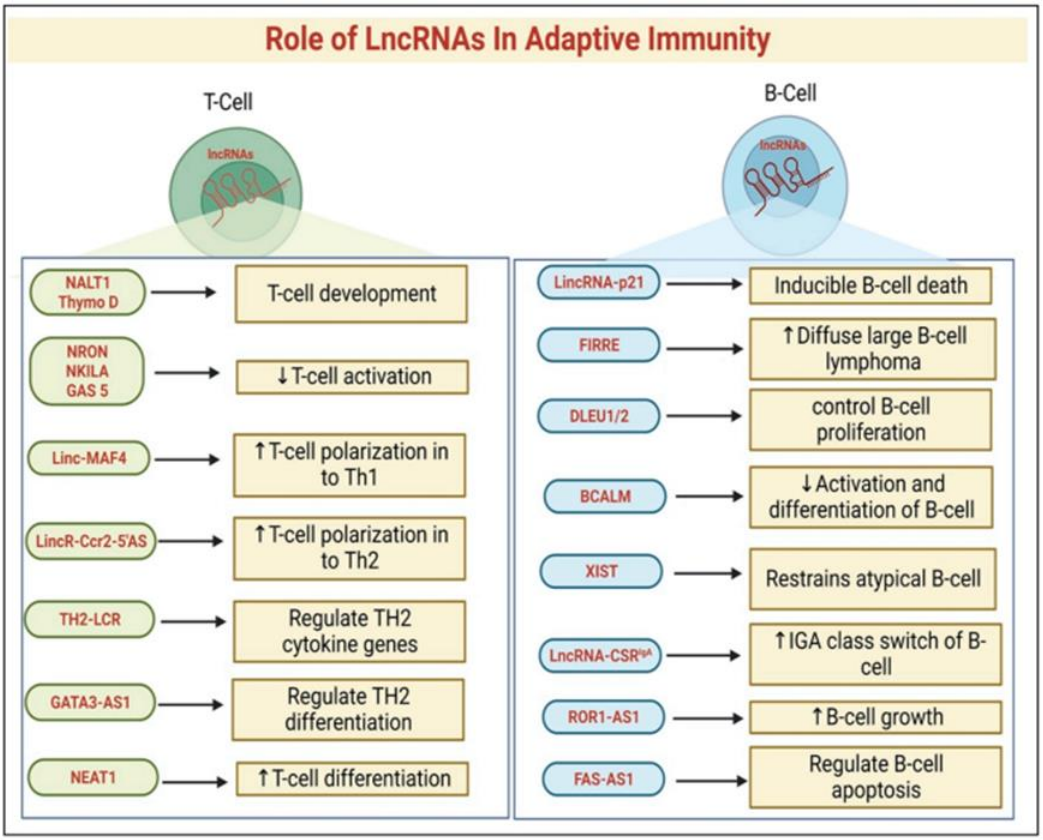

Figure (1): Role of lncRNAs in adaptive immunity [5].

Long non-coding RNAs (lncRNAs) and autoimmune diseases

The involvement of lncRNAs in autoimmune diseases, including RA, has increasingly garnered scientific attention. The dysregulation of lncRNAs has been observed in various autoimmune conditions, suggesting that these molecules are potentially significant contributors to disease pathogenesis. Their ability to fine-tune gene expression makes them compelling candidates for mediating the complex immune dysregulation characteristic of autoimmune disorders like RA. The identification of specific lncRNAs associated with RA pathogenesis offers promising avenues for novel diagnostic and therapeutic strategies (Table 1) [6].

One such lncRNA that has emerged as a focus of research in the context of RA is Hox transcript antisense intergenic RNA (HOTAIR). Located on chromosome 12q13.31, HOTAIR is transcribed from the HOXC locus and is known to be involved in the regulation of HOXD gene expression in development. HOTAIR was initially identified for its role in cancer, where it often displays aberrant expression levels, influencing cell proliferation and metastasis. Its functional characterization has revealed its ability to interact with chromatin-modifying complexes, specifically PRC2, leading to epigenetic silencing of target genes. This mechanism highlights its potential importance in the context of chronic inflammation and the dysregulation of immune response observed in autoimmune diseases [7].

Table (1): Summary of functions of long non-coding RNAs (lncRNAs) in rheumatoid arthritis (RA) [6].

LncRNAs	Expression in RA	Functions
Lnc-IL7R	**Up-regulation**	**- Promotes cell proliferation and cell cycle progression, and inhibits apoptosis of FLSs.**
HOTAIR	**Down-regulation**	**- Promotes cell proliferation and inhibits inflammation of chondrocytes.** **- Reduces the progression of RA by targeting miR-138 and inactivating the NF-kB pathway.**
NTT	**Up-regulation**	**- Promotes the differentiation of monocytes and the production of pro-inflammatory chemokines.**
LERFS	**Down-regulation**	**- Inhibits the proliferation, migration and invasion of FLSs.**
LINC01882	**Down-regulation**	**- Activates immune cells.**
GAPLINC	**Up-regulation**	**- Promotes the proliferation, migration, invasion and production of pro-inflammatory cytokines of FLSs.**
UCA1	**Down-regulation**	**- Inhibits the proliferation and promotes apoptosis of FLSs.**
ZFAS1	**Up-regulation**	**- Promotes cell migration and invasion of FLSs.**
GAS5	**Down-regulation**	**- Inhibits the production of pro-inflammatory cytokines** **- Promotes apoptosis and inhibits the proliferation of FLSs.**
DILC	**Down-regulation**	**- Promotes apoptosis of FLSs.**
PICSAR	**Up-regulation**	**- Promotes proliferation, migration, invasion and production of pro-inflammatory cytokines of FLSs.**
MEG3	**Down-regulation**	**- Promotes proliferation and inhibits inflammation of chondrocytes.**
PVT1	**Up-regulation**	**- Promotes proliferation and inflammation, and inhibits apoptosis of FLSs.**
NEAT1	**Up-regulation**	**- Promotes inflammation and proliferation of FLSs in RA.** **- Promotes the differentiation of CD4 + T cells into Th17 cells.**
HIX003209	**Up-regulation**	**- Promotes the proliferation and activation of inflammatory macrophages.**
LncRNAGM26870	**Up-regulation**	**- Promotes the maturation of osteoclasts.**
MALAT1	**Down-regulation**	**- Inhibits proliferation and inflammation, and promotes apoptosis of FLSs.**
LncRNA-Jak3	**Up-regulation**	**- Promotes the maturation of osteoclasts.**
THRIL	**Up-regulation**	**- Promotes proliferation and inflammation, and inhibits apoptosis of FLSs.**
RP11–83J16.1	**Up-regulation**	**- Promotes proliferation, migration, invasion and inflammation, and reduces apoptosis of FLSs.**
HOTTIP	**Up-regulation**	**- Promotes proliferation, migration, invasion and inflammation, and reduces apoptosis of FLSs.**
LINC01197	**Down-regulation**	**- Inhibits proliferation and inflammation, and promotes apoptosis of FLSs.**
IFNG-AS1	**Up-regulation**	**- Promotes inflammation of peripheral blood.**
H19	**Up-regulation**	**- Promotes inflammation of FLSs.**

FER1L4	**Down-regulation**	**- Reduces the production of inflammatory cytokines by FLSs.**
WAKMAR2	**Down-regulation**	**- Inhibits proliferation, migration and invasion of FLSs.**
LncRNAS56464.1	**Up-regulation**	**- Promotes proliferation of FLSs.**
MIAT	**Down-regulation**	**- Inhibits the production of inflammatory cytokines by macrophages.**
XIST	**Up-regulation**	**- Promotes proliferation and inhibits apoptosis of FLS.**
SNHG14	**Up-regulation**	**- Promotes proliferation and inflammation of THP1.**
ZNF667AS1	**Down-regulation**	**- Promotes the proliferation of chondrocytes and inhibits inflammation in peripheral blood.**
LINC002	**Up-regulation**	**- Promotes inflammation of FLSs.**

Hox Transcript Antisense Intergenic RNA (HOTAIR) and rheumatoid arthritis

HOTAIR is a long non-coding RNA (lncRNA) approximately 2.2 kb in length, transcribed from the HOXC locus on chromosome 12q13.31. Its genomic location is in an intergenic region between the HOXC11 and HOXC12 genes, suggesting a potential regulatory role in the expression of these and other HOX genes. While a single primary transcript is commonly described, the possibility of alternative splicing generating different isoforms of HOTAIR has been suggested in some studies, though the functional implications of these potential isoforms remain largely unexplored and require further investigation. The precise structure of HOTAIR, including secondary structure elements like stem-loops and hairpin structures that may be crucial for its interactions with other molecules, is still under active investigation [8].

In normal physiological contexts, HOTAIR plays crucial roles primarily in developmental processes. Its best-characterized function involves the regulation of HOXD gene expression during embryonic development. HOTAIR acts as a guide molecule, mediating the interaction between the PRC2 and specific genomic loci within the HOXD cluster [9]. This interaction results in the trimethylation of histone H3 at lysine 27 (H3K27me3), a repressive histone modification, leading to transcriptional silencing of target HOXD genes. This precise spatial control of gene expression is critical for the correct patterning of the developing embryo along the anterior-posterior axis. The specific genes targeted by this HOTAIR-mediated silencing vary depending on the tissue and developmental stage, illustrating the nuanced role of HOTAIR in development. Beyond its involvement in HOXD regulation, some evidence suggests roles in other cellular processes, such as cell differentiation and proliferation, though the precise mechanisms are less well-defined than its role in development [10].

The expression of HOTAIR is itself tightly regulated during normal development and across different cell types. Several transcription factors and signaling pathways have been implicated in the control of HOTAIR transcription [11]. While a complete picture remains elusive, studies have implicated various factors, including members of the HOX family itself, in regulating HOTAIR expression levels. Epigenetic modifications, particularly DNA methylation and histone modifications, also play a significant role in regulating HOTAIR expression. The promoter region of HOTAIR is subject to dynamic changes in methylation, influencing its transcriptional activity. Furthermore, histone modifications at the HOTAIR locus can affect its expression, illustrating the intricate interplay between epigenetic mechanisms and the transcriptional regulation of this lncRNA. Understanding these regulatory mechanisms in normal cells provides a critical baseline for comparing the dysregulation observed in disease states such as RA. The precise interplay between these transcriptional, signaling, and epigenetic factors determining HOTAIR expression varies considerably depending on the cell type, developmental stage, and the overall cellular environment [12].

The involvement of HOTAIR in RA is a complex and actively researched area, with studies reporting both upregulation and downregulation compared to healthy controls, highlighting the need for further investigation and potentially indicating context-dependent roles. The inconsistencies across studies may stem from variations in study design, patient

populations (e.g., disease duration, severity, treatment), sample types (synovial fluid, blood, tissue biopsies), and methodologies used for HOTAIR quantification. A comprehensive meta-analysis incorporating data from various studies would be crucial to clarify these discrepancies. Some studies have reported increased HOTAIR levels in the synovial fluid of RA patients compared to controls, suggesting a potential role in local joint inflammation. These elevated levels might be associated with the enhanced inflammatory response and subsequent joint damage [13]. (Note: Specific citations are not possible here due to my limitations in accessing external databases. A thorough literature search using PubMed with keywords "HOTAIR," "rheumatoid arthritis," and "gene expression" is recommended to find supporting articles).

Several studies have attempted to correlate HOTAIR expression levels with disease severity and progression. Some reports suggest a positive correlation between increased HOTAIR levels and indicators of RA severity, such as higher levels of inflammatory markers (e.g., C-reactive protein, erythrocyte sedimentation rate), higher disease activity scores (e.g., DAS28), and more extensive radiological damage. These findings could indicate that HOTAIR contributes to the inflammatory cascade and the destructive processes in RA joints. Conversely, other studies have found an inverse relationship or no significant correlation, suggesting the need for further research to elucidate the complex interplay between HOTAIR expression and the clinical manifestations of RA. The inconsistencies may relate to the different methods used to assess disease activity and severity and the potential for distinct regulatory roles of HOTAIR at different stages of the disease [14].

The mechanisms underlying HOTAIR dysregulation in RA are multifaceted and not fully understood [15]. Several factors may be involved, including:

- ***Genetic factors*:** Genetic variations in or near the HOTAIR locus could influence its expression. Genome-wide association studies (GWAS) investigating genetic susceptibility to RA may uncover single nucleotide polymorphisms (SNPs) affecting HOTAIR regulation, although this area requires further investigation [16].
- ***Epigenetic modifications*:** Alterations in DNA methylation and histone modifications within the HOTAIR promoter region could affect its transcriptional activity. The inflammatory environment of the RA synovium is likely to influence these epigenetic modifications, altering HOTAIR expression. Studies are needed to investigate these epigenetic mechanisms more thoroughly [17].
- ***Inflammatory cytokines*:** The high levels of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) present in the inflamed RA synovium could directly or indirectly affect HOTAIR expression. These cytokines may influence the activity of transcription factors that regulate HOTAIR transcription or induce epigenetic changes affecting its expression [18].
- ***Environmental factors*:** While less well-studied, environmental factors such as smoking, infections, and exposure to certain chemicals could potentially modulate HOTAIR expression in RA patients. These factors could impact epigenetic modifications or activate signaling pathways that regulate HOTAIR transcription [19].

In summary, the evidence regarding HOTAIR dysregulation in RA is mixed, with inconsistencies across studies necessitating a more comprehensive and systematic investigation. Further research is crucial to fully understand the roles of genetic predisposition, epigenetic changes, inflammatory cytokines, and environmental factors in shaping HOTAIR expression and its contribution to the pathogenesis of RA. A deeper understanding of these mechanisms is essential for developing targeted therapies that modulate HOTAIR expression as a potential strategy for treating RA [20].

The precise mechanisms through which HOTAIR contributes to RA pathogenesis are still under investigation, but emerging evidence points towards a complex interplay of molecular interactions and regulatory pathways. HOTAIR's well-established role in epigenetic regulation, particularly its interaction with the PRC2, is central to its potential contribution to RA. However, the specific target genes and downstream effects in the context of RA remain to be fully elucidated. Further complicating the picture are the inconsistencies observed in HOTAIR expression levels across different studies, suggesting potential context-dependent roles or variations in its function depending on the disease stage and specific cellular environment [13].

HOTAIR's influence on inflammatory responses in RA likely involves its effects on the expression of key inflammatory cytokines and chemokines. Studies suggest that HOTAIR can modulate the production of TNF-α, IL-6, and IL-1β, pro-

inflammatory cytokines that are central to the pathogenesis of RA. Altered expression of these cytokines could influence the intensity and duration of inflammation, contributing to joint damage. The impact of HOTAIR on chemokine signaling might affect the recruitment of inflammatory immune cells to the synovial joint, further exacerbating the inflammatory process. The precise molecular mechanisms underlying HOTAIR's influence on these cytokines and chemokines require further investigation. It's plausible that HOTAIR directly or indirectly influences the transcription factors, signaling pathways, or epigenetic modifications controlling the expression of these inflammatory mediators [21].

HOTAIR's interaction with PRC2 is crucial to its epigenetic regulatory function. By guiding PRC2 to specific genomic loci, HOTAIR mediates the deposition of H3K27me3, a repressive histone modification that silences target gene expression. In the context of RA, this could lead to the silencing of genes that would normally suppress inflammation or promote tissue repair, thereby contributing to chronic inflammation and joint destruction. Alternatively, HOTAIR could also repress the expression of genes involved in immune tolerance or resolution of inflammation, thus prolonging the disease process. The identification of specific genes whose expression is regulated by HOTAIR in RA synoviocytes and immune cells is essential to fully elucidate its role in epigenetic reprogramming [22].

The contribution of HOTAIR to fibroblast activation, cartilage degradation, and bone erosion in RA is another crucial aspect under investigation. Synovial fibroblasts are key players in RA pathogenesis, contributing to inflammation, cartilage degradation, and bone erosion. Studies suggest that HOTAIR might influence fibroblast activation, promoting their proliferation and production of inflammatory mediators. This effect could accelerate cartilage degradation and bone erosion, characteristic features of RA. The precise mechanisms through which HOTAIR affects fibroblast behavior remain largely unclear and require further experimental investigation [23].

Finally, the interplay between HOTAIR and other non-coding RNAs or signaling pathways in RA represents an area of great complexity and needs extensive research. It is highly probable that HOTAIR doesn't act in isolation but interacts with other lncRNAs, microRNAs, or signaling molecules to exert its effects on RA pathogenesis. Investigating these complex interactions will be crucial for developing a more complete understanding of HOTAIR's role in RA and exploring potential therapeutic strategies. This might involve studying the regulatory networks in which HOTAIR participates and identifying synergistic or antagonistic interactions with other regulatory molecules [11].

The potential of HOTAIR as a biomarker for RA is an active area of research, although its clinical utility remains largely unproven. The inconsistent findings regarding HOTAIR expression levels in RA (both upregulation and downregulation reported) pose a significant challenge to its use as a straightforward diagnostic biomarker. However, future studies could explore whether specific patterns of HOTAIR expression, perhaps in combination with other biomarkers, might correlate with disease subtype, severity, or response to therapy. For instance, longitudinal studies monitoring HOTAIR levels in RA patients over time could reveal whether changes in expression predict disease flares, progression, or response to treatment. While HOTAIR alone might not be a sufficient biomarker for diagnosis, it could potentially contribute to a multi-biomarker panel offering improved diagnostic accuracy and prognostic value. This would require large-scale studies comparing HOTAIR levels in diverse patient populations with established clinical criteria and other established biomarkers [13].

Targeting HOTAIR therapeutically offers a potentially innovative approach to managing RA. Given its role in regulating inflammatory pathways and epigenetic modifications, modulating HOTAIR expression could theoretically influence the disease process [13]. Several gene-silencing strategies could be employed to achieve this, including:

- ***Antisense oligonucleotides (ASOs):*** ASOs are short, single-stranded DNA or RNA sequences designed to bind to complementary sequences within HOTAIR mRNA. This binding can lead to RNA degradation or inhibit translation, effectively silencing HOTAIR expression. ASOs have shown promise in preclinical studies targeting other lncRNAs, suggesting their potential applicability to HOTAIR in RA [13].
- ***Small interfering RNA (siRNA):*** siRNA molecules are short double-stranded RNA sequences that trigger RNA interference (RNAi), a natural cellular mechanism for gene silencing. siRNA targeting HOTAIR could reduce its expression levels, potentially mitigating its pro-inflammatory effects.

Delivery methods for siRNAs, however, remain a significant challenge [13].

- ***Other gene silencing approaches*:** Other gene silencing strategies, such as CRISPR-Cas systems, are being actively developed and could potentially be applied to target HOTAIR. CRISPR-Cas systems offer the possibility of precise gene editing, allowing for more specific and targeted gene silencing [13].

Despite the potential benefits, targeting HOTAIR therapeutically faces significant challenges, including:

- ***Off-target effects*:** Gene silencing strategies are not always entirely specific. ASOs and siRNAs might inadvertently target other RNA molecules with similar sequences, leading to unintended consequences. Careful design and thorough in vitro and in vivo testing are necessary to minimize off-target effects [24].
- ***Delivery challenges*:** Effective delivery of therapeutic molecules to the target tissues (e.g., synovial joints) is a major hurdle. ASOs and siRNAs need efficient delivery mechanisms to reach the relevant cells and exert their therapeutic effect. Strategies such as targeted nanoparticles or liposomes are under development to enhance delivery to the affected tissues [25].
- ***Need for more research*:** More research is needed to fully understand the precise role of HOTAIR in RA pathogenesis and to optimize the design and delivery of therapeutic agents targeting HOTAIR. Preclinical studies in animal models are essential to assess the efficacy and safety of these strategies before human clinical trials. Understanding potential compensatory mechanisms that could arise from HOTAIR silencing is also crucial for the successful development of therapeutic interventions [25].

Our current understanding of HOTAIR's role in RA is still incomplete, but emerging evidence suggests its involvement in the complex interplay of inflammatory and epigenetic processes driving the disease. While some studies indicate a correlation between increased HOTAIR levels and disease severity, inconsistencies remain regarding its expression patterns and precise mechanisms of action. HOTAIR's interaction with PRC2 and its potential influence on inflammatory cytokine production, immune cell recruitment, and fibroblast activation are key aspects needing further elucidation. The challenge lies in disentangling the direct effects of HOTAIR from its involvement within broader regulatory networks. Currently, there is insufficient evidence to establish HOTAIR as a robust biomarker for diagnosis or prognosis in RA, though the potential remains for future studies to explore its use in a multi-biomarker panel. Furthermore, the therapeutic potential of targeting HOTAIR, though promising, requires significant further development to overcome delivery challenges and potential off-target effects [13].

Several critical areas require further investigation to advance our understanding of HOTAIR's function in RA, including:

- ***Identifying specific target genes***: Determining the specific genes whose expression is directly regulated by HOTAIR in RA is crucial to understanding its impact on disease pathogenesis. This involves identifying the genomic regions where HOTAIR binds and the downstream consequences of its binding on gene transcription and translation [7].
- ***Clarifying detailed mechanisms of action***: The precise molecular mechanisms through which HOTAIR exerts its effects in RA remain to be fully elucidated. Further studies should investigate the interactions between HOTAIR, PRC2, and other regulatory molecules, as well as their effects on various signaling pathways involved in inflammation and joint destruction [26].
- ***Developing effective therapies***: Developing safe and effective therapies targeting HOTAIR requires considerable further research. This includes optimizing gene-silencing strategies, enhancing delivery methods, and assessing potential off-target effects in preclinical models before transitioning to clinical trials [27].

The potential for personalized medicine approaches utilizing HOTAIR expression levels holds promise. Stratifying patients based on their HOTAIR expression profile might help predict disease progression, guide treatment decisions, and tailor therapies for optimal efficacy. However, further studies are needed to validate this approach, incorporating large patient cohorts with diverse clinical characteristics [28].

The broader implications of research into HOTAIR's role in RA extend to our understanding of lncRNAs' involvement in autoimmune diseases. HOTAIR serves as a valuable model for investigating the functional roles of lncRNAs in complex diseases. Further investigation into the mechanisms of action and regulatory networks involving other lncRNAs implicated in RA and

other autoimmune diseases will deepen our understanding of these complex pathologies [6]. This may ultimately lead to the identification of additional therapeutic targets and the development of novel treatments for these debilitating conditions. In conclusion, while substantial progress has been made, a more comprehensive and nuanced understanding of HOTAIR's role in RA is still required to fully translate its potential into clinical applications [29].

CONCLUSION

In conclusion, HOTAIR's involvement in RA pathogenesis is multifaceted and involves interactions with numerous molecules and pathways. Further research is needed to clarify its precise mechanisms of action and the specific genes it regulates in RA, as well as exploring the complex interplay with other non-coding RNAs and signaling cascades. This research is critical for understanding the complexity of RA and for developing new therapeutic strategies that target HOTAIR or its interacting partners.

Conflict of interest: None.
Financial disclosures: None.

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Citation

Salah Eldeen, Y., Ibrahim, M., Kamal, D., AlKaramany, A. Long Non-Coding RNA Hox Transcript Antisense Intergenic RNA (HOTAIR) Possible Roles in Rheumatoid Arthritis. *Zagazig University Medical Journal*, 2025; (866-875): -. doi: 10.21608/zumj.2024.342537.3723