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Long non-coding RNA RMRP in Autoimmune Diseases: A Systematic Review

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Abstract:

Long non-coding RNAs (lncRNAs) are a recently identified group of non-coding RNAs that do not include instructions for protein synthesis. These RNAs possess many crucial regulatory roles. The aberrant expression of lncRNAs has been related to several illnesses' clinical progression, making them potential candidates for diagnostic biomarkers. The current study aimed to evaluate lncRNAs RMRP may be considered as a diagnostic marker in autoimmune diseases. Our search results from PubMed, Medline, and EMBASE included original studies. Review papers were not included. Researchers published one or more lncRNA, that were found in their experiments. The study found elevated expression levels of RMRP (RNA Component of Mitochondrial RNA Processing Endoribonuclease) and FLICR (FOXP3 Regulating Long Intergenic Non-Coding RNA) in multiple sclerosis (MS)cases, with FLICR being effective in distinguishing between patients and healthy controls. However, RMRP expression in peripheral blood showed insignificant increases, suggesting RMRP may play a crucial role in chondrocyte hypertrophy. Regarding these findings, lncRNAs RMRP may be considered as diagnostic markers in autoimmune diseases.

Keywords: Long non-coding RNA; RMRP; Autoimmune Diseases.

1. Introduction

Autoimmune diseases rank as the third most widespread category of illnesses, behind cancer and cardiovascular disorders. This disease is characterized by its intricate nature, which arises from the interplay among genetic and environmental factors [1,

2]. Management of autoimmune illness might be linked to an ongoing puzzle being assembled. Treatment options for autoimmune diseases encompass a range of therapies, such as physical therapy, corticosteroids, NSAID, anti-cytokine therapies, disease-modifying anti-inflammatory drugs, inhibition of intracellular signaling pathways, suppression of co-stimulation, biological agents that suppress T cell function, depletion of B cells and induction of energy, as well as the use of regulatory T cells [3, 4].

Autoimmune diseases encompass several complex conditions such as rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, idiopathic inflammatory myopathy, systemic sclerosis, and Sjögren's syndrome. Clinical presentations of these diseases can range from mild skin rashes to severe dysfunction of multiple organs. Due to the intricate and incompletely understood nature of the pathological process underlying autoimmune disorders, doctors have difficulties in promptly diagnosing and effectively treating most autoimmune diseases [5-10].

Noncoding regulatory elements, translated into noncoding RNA (ncRNA), have substantial regulatory functions in complex organisms between 1-5% of the whole genome is responsible for generating proteins. lncRNAs are a group of ncRNAs that have a length exceeding 200 nucleotides. They may be categorized into two types based on their functions: structural (associated with translation) and regulatory lncRNAs. Current research elucidated the significance of ncRNAs in governing numerous fundamental biological processes, including growth, differentiation, and cellular metabolism [8, 10].

LncRNAs play significant roles in immune-related disorders such as inflammatory and autoimmune diseases. They regulate the formation, homeostasis, and function of the innate and adaptive immune system by controlling the activity of innate immune cells and lymphocytes [11].

Recent research has indicated that long non-coding RNAs (lncRNAs) may be released into the bloodstream and remain stable in bodily fluids such as blood and urine. These circulating lncRNAs have the potential to be used as diagnostic biomarkers for many disorders. Outside of cells, these molecules are mostly found in exosomes, which increase their concentration and resistance to degradation by RNases, serving as exosome lncRNA molecules [12, 13]. Exosomes are small vesicles, with a size in

the nanometer range, that may be secreted by many cells, including immune cells, into body fluids. Furthermore, they participate in several cellular processes such as immune system regulation, signal transduction, and antigen presentation. Several researchers have suggested that exosomes and their physiologically active cargos, such as lncRNAs, have the potential to be valuable for diagnostic purposes. Exosomes containing lncRNAs can modify and replace biological data and convey biological signals. RNA component of mitochondrial RNA processing endoribonuclease (RMRP) is a transcript with wide expression in diverse tissues obtained from human and mouse species [14]. Our study aimed to evaluate lncRNAs RMRP as a diagnostic marker in autoimmune diseases.

2. Methods

2.1. Literature search

Inclusion criteria

RCT studies, controlled clinical trials, retrospective cohort studies, and studies published in English.

Exclusion criteria

Non-English, duplicates, non-clinical outcomes, case reports, case series, review articles, cross-sectional, abstract, non-full text, cadaver, model, data set, and overlapping were excluded.

2.2. Statistical considerations

The results from the involved studies were consolidated using systematic review management software, ensuring each study met the predefined inclusion criteria. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart was developed to explain the process of selecting studies for inclusion in the review (Figure 1). That chart consisted of information regarding the number of studies screened, reviewed for eligibility, and involved in the review. The technique, developed by the Cochrane Collaboration for evaluating the risk of bias, was utilized to assess the potential for bias in each trial included in the analysis. That involved examining aspects such as randomization, blinding, and the completeness of outcome reporting. Heterogeneity, among study results, was assessed by I^2 statistics. Sensitivity analyses were performed to explore the impacts of varying methodologies and participant

characteristics on the overall results. Publication bias was also assessed, using methods such as funnel plots and Egger's regression test, to determine the influence of unpublished studies on the review's findings.

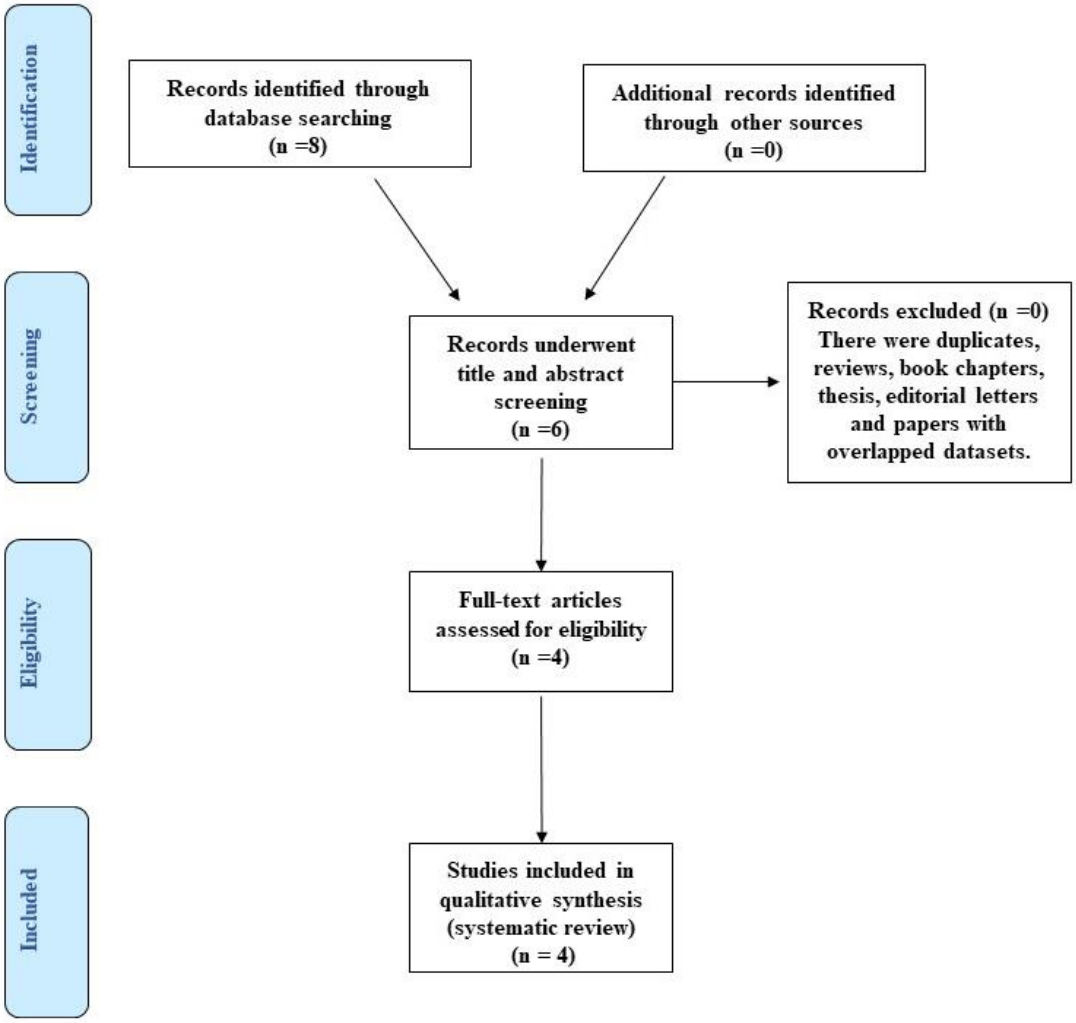

Figure 1: PRISMA flow diagram showing the process of study selection.

3. Results

Four studies were included, three were case-control studies and one experimental study. A total of 328 participants were included in the searched studies. They were divided into cases and control groups with a mean age was 38.3

years as shown in **Table 1**. Autoimmune dermatological disease and RMRP expression in the included studies as shown in **Table 2.**

Table 1: Studies characteristics.

Study	Year	Type of the study	Number	Age
Dadyar et al. [15]	2022	Case-control	50 patients / 50 control	41.8
Yang et al. [16]	2021	Case-control	56 patients /32 control	38.6/38.3
Ghaiad et al. [17]	2020	Case-control	72 cases / 28 control	34 /39
Steinbusch et al. [18]	2017	Experimental		

Table 2: Autoimmune disease and RMRP expression.

Author	Year	Disease	RMRP expression
Dadyar et al. [15]	2022	Multiple sclerosis (MS)	• The levels of RMRP and FLICR expression were much higher in individuals with multiple sclerosis (MS) as compared to the control group. • ROC curve analysis revealed the appropriate power of FLICR in differentiating between MS cases and healthy controls (AUC value=0.84). • RMRP, NEST, TH2-LCR and MAFTRR had AUC values of 0.63, 0.57, 0.53 and 0.52, respectively.
Yang et al. [16]	2021	Still's disease	• The levels of RMRP distinguished people with Adult-onset Still's disease (AOSD) from individuals without the condition (OR 1.73, 95% CI 1.12–2.69, p <0.05).
Ghaiad et al. [17]	2020	Multiple sclerosis (MS)	• Expression of RMRP was evaluated in the peripheral blood of individuals with MS for 1st time (p <0.05). • No statistically significant variations were detected between relapse and remission groups for RMRP, IFNG-AS, and IFN-γ levels. • The serum levels were 5 ± 1.8 in control vs 6.5 ± 3.9 in cases.

Steinbusch et al. [18]	2017	Chondrocyte hypertrophy (CHH)	• The expression of RMRP RNA is controlled at several phases of chondrogenic development, suggesting that RMRP RNA may have a crucial function in chondrocyte hypertrophy, which might have significant implications for the pathobiology of CHH.

4. Discussion

The human genome project's completion and advancement of high-throughput genomic sequencing technology have led to a growing interest in ncRNA. Prior research has unexpectedly shown that while most of the human genome undergoes transcription, less than 2% is responsible for protein encoding, whereas the rest is responsible for encoding ncRNAs [19]. For an extended period, ncRNAs, which make up the majority of different transcripts, have been regarded as the byproduct generated during transcription and have been disregarded. Recent human genome-wide association studies (GWASs) have revealed that over 90% of illness-related SNPs are linked to noncoding regions of the genome. That suggests that mutations in ncRNAs might potentially account for some disease characteristics [20, 21]. Of all the different types of ncRNAs, lncRNAs have lately emerged as a primary area of study about illnesses, particularly autoimmune diseases.

In 2002, lncRNAs were identified as a novel type of transcript after the extensive sequencing of whole murine cDNA libraries. These transcripts are at least 200 nucleotides long and cannot code for proteins. The majority of lncRNAs are transcribed by RNA polymerase (Pol) II/Pol I, whereas a subset is transcribed by RNA Pol III [22].

There are over 100,000 lncRNAs in humans. LncRNAs are often expressed at lower levels in contrast to mRNAs, which poses challenges in their identification and analysis. Recent research revealed that most lncRNAs display little conservation in their main sequence. However, several lncRNAs are reported to establish highly conserved RNA secondary structures, which play a role in coordinating interactions between RNA molecules, RNA and proteins, and RNA and DNA [15].

lncRNAs are tightly controlled and selectively produced in many organs, tissues, cell types, and subcellular compartments.

Furthermore, levels of lncRNAs fluctuate throughout various phases of development or states of disease. That indicates that lncRNAs have crucial roles in controlling cellular activities and advancing diseases. Indeed, several lncRNAs have been revealed to have a role in the causation of various human disorders [18-20].

lncRNAs are commonly classified depend on their spatial relationship to adjacent protein-coding genes, namely as intergenic, antisense, intronic, or bidirectional. Intergenic lncRNAs, known as large intervening noncoding RNAs or lincRNAs, are lncRNAs situated among protein-coding genes and have distinct transcriptional units. Antisense lncRNAs refer to long non-coding RNAs produced in the opposite direction of adjacent protein-coding genes and cover at least one exon. Intronic lncRNAs are long non-coding RNAs derived from intronic regions and do not overlap with exons. Bidirectional lncRNAs are transcripts that originate diversely from the promoter of adjacent protein-coding genes [23].

Regarding our results, four studies were included, three were case-control studies and one experimental study. A total of 328 participants were included. They were divided into case and control groups with a mean age of 38.3 years.

Regarding our findings, Autoimmune disease and RMRP expression, Autoimmune diseases included multiple sclerosis, stills disease and chondrocyte hypertrophy. Dadyar et al., (2022) revealed that expression level of RMRP was greater in individuals with MS in contrast to controls [15]. ROC curve analysis demonstrated that FLICR had a suitable ability to distinguish between MS cases and healthy controls, with an AUC value of 0.84. The AUC values for RMRP, NEST(IFNG-AS1), TH2-LCR (Th2 Cytokine Locus Control Region) and MAFTRR (MAF Transcriptional Regulator RNA) were 0.63, 0.57, 0.53, and 0.52, respectively. Yang et al., (2021) showed that levels of RMRP could distinguish Adult-onset Still's disease (AOSD) cases with Stills disease from healthy controls (OR 1.73, 95 percent CI 1.12–2.69, p <0.05) [16].

Ghaiad et al., (2021) showed that the expression of RMRP was evaluated in the peripheral blood of MS individuals for 1st time, revealing a statistically insignificant elevation in levels [17].

Minimal alterations in IFN-γ, IFNG-AS, and RMRP were detected when comparing the recurrence and remission groups in this study

Steinbusch al., (2017) revealed that expression of RMRP RNA is controlled at several phases of chondrogenic differentiation,

suggesting that RMRP RNA may have a crucial function in the enlargement of chondrocytes, which might have significant implications for the pathobiology of chondrocyte hypertrophy (CHH) [18].

The research done by Mehmandar-Oskuie et al. (2023) reported that SLE is a persistent autoimmune disorder that mostly impacts women in their reproductive years, leading to harm to several organs and systems. The cause of the condition is intricate and includes genetic vulnerability, external influences, and disruptions in the immune system. There is evidence indicating that lncRNAs may play a role in the development of SLE. The expression patterns of lncRNAs in people with SLE differ from those in healthy individuals, and these differences may be associated with the severity of the disease. The authors examined recent research on various methods of using lncRNAs for diagnosing and treating autoimmune disorders in humans. They also discussed the present difficulties in developing lncRNA-based therapies for autoimmune diseases [23].

Conclusion

We concluded that lncRNA RMRP could be considered a diagnostic marker in autoimmune diseases. Further prospective studies are needed to confirm these results.

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Conflicts of Interest: All authors declare they have no conflicts of interest.

References

1. Bieber K, Hundt JE, Yu X, Ehlers M, Petersen F, Karsten CM, Köhl J, Kridin K, Kalies K, Kasprick A, Goletz S. Autoimmune pre-disease. Autoimmunity Reviews. 2023; 22(2):103236. doi: 10.1016/j.autrev.2022.103236.
2. Niccolai E, Boem F, Emmi G, Amedei A. The link "Cancer and autoimmune diseases" in the light of microbiota: Evidence of a potential culprit. Immunology letters. 2020;222:12-28. Doi: 10.1016/j.imlet.2020.03.001
3. Kucuksezer UC, Aktas Cetin E, Esen F, Tahrali I, Akdeniz N, Gelmez MY, Deniz G. The role of natural killer cells in autoimmune diseases. Frontiers in immunology. 2021;12:622306. doi: 10.3389/fimmu.2021.622306
4. Moran CA, Collins LF, Beydoun N, Mehta PK, Fatade Y, Isiadinso I, Lewis TT, Weber B, Goldstein J, Ofotokun I, Quyyumi A. Cardiovascular implications of immune disorders in women. Circulation Research. 2022;130(4):593-610. DOI: 10.1161/CIRCRESAHA.121.319877.
5. Negrini S, Emmi G, Greco M, Borro M, Sardanelli F, Murdaca G, Indiveri F, Puppo F. Sjögren's syndrome: a systemic autoimmune disease. Clinical and experimental medicine. 2022;22(1):9-25. doi: 10.1007/s10238-021-00728-6.

6. Ferri C, Arcangeletti MC, Caselli E, Zakrzewska K, Maccari C, Calderaro A, D'Accolti M, Soffritti I, Arvia R, Sighinolfi G, Artoni E. Insights into the knowledge of complex diseases: Environmental infectious/toxic agents as potential etiopathogenetic factors of systemic sclerosis. Journal of Autoimmunity. 2021;124:102727. doi: 10.1016/j.jaut.2021.102727.
7. Murdaca G, Greco M, Borro M, Gangemi S. Hygiene hypothesis and autoimmune diseases: A narrative review of clinical evidences and mechanisms. Autoimmunity Reviews. 2021;20(7):102845. doi: 10.1016/j.autrev.2021.102845.
8. Karimi B, Firoozabadi AD, Peymani M, Ghaedi K. Circulating long noncoding RNAs as novel bio-tools: Focus on autoimmune diseases. Human Immunology. 2022;83(8-9):618-27. doi: 10.1016/j.humimm.2022.06.001.
9. Zou Y, Xu H. Involvement of long noncoding RNAs in the pathogenesis of autoimmune diseases. J Transl Autoimmun. 2020;3:100044. doi: 10.1016/j.jtauto.2020.100044.
10. Tsai CY, Hsieh SC, Wu TH, Li KJ, Shen CY, Liao HT, Wu CH, Kuo YM, Lu CS, Yu CL. Pathogenic roles of autoantibodies and aberrant epigenetic regulation of immune and connective tissue cells in the tissue fibrosis of patients with systemic sclerosis. International journal of molecular sciences. 2020;21(9):3069. doi: 10.3390/ijms21093069.
11. Lao MX, Xu HS. Involvement of long non-coding RNAs in the pathogenesis of rheumatoid arthritis. Chinese medical journal. 2020;133(08):941-50. doi: 10.1097/CM9.0000000000000755.
12. Zhai X, Zhang Y, Xin S, Cao P, Lu J. Insights into the involvement of circular RNAs in autoimmune diseases. Frontiers in Immunology. 2021;12:622316. doi: 10.3389/fimmu.2021.622316.
13. Tofigh R, Hosseinpourfeizi M, Baradaran B, Teimourian S, Safaralizadeh R. Rheumatoid arthritis and non-coding RNAs; how to trigger inflammation. Life Sciences. 2023;2023:121367. doi: 10.1016/j.lfs.2023.121367.
14. Wu X, Xiao Y, Ma J, Wang A. Circular RNA: A novel potential biomarker for skin diseases. Pharmacological research. 2020;158: 104841. doi: 10.1016/j.phrs.2020.104841.
15. Dadyar M, Hussen BM, Eslami S, Taheri M, Emadi F, Ghafouri-Fard S, Sayad A. Expression of T cell-related lncRNAs in multiple sclerosis. Frontiers in Genetics. 2022;13:967157. doi: 10.3389/fgene.2022.967157.
16. Yang CA, Chen PK, Lan JL, Chang CK, Chang JG, Chang SH, Lin CC, Chen DY. Expression signature of inflammation-associated long non-coding RNAs in adult-onset Still's disease. Clin. Exp. Rheumatol. 2021;39: 67-74. doi: 10.55563/clinexprheumatol/4jx6zy.
17. Ghaiad HR, Elmazny AN, Nooh MM, El-Sawalhi MM, Shaheen AA. Long noncoding RNAs APOA1-AS, IFNG-AS1, RMRP and their related biomolecules in Egyptian patients with relapsing-remitting multiple sclerosis: Relation to disease activity and patient disability. J Adv Res. 2019;21:141-150. doi: 10.1016/j.jare.2019.10.012.
18. Steinbusch MMF, Caron MMJ, Surtel DAM, Friedrich F, Lausch E, Pruijn GJM, Verhesen W, Schroen BLM, van Rhijn LW, Zabel B, Welting TJM. Expression of RMRP RNA is regulated in chondrocyte hypertrophy and determines chondrogenic differentiation. Sci Rep. 2017;7(1):6440. doi: 10.1038/s41598-017-06809-5.
19. Pers JO, Vlachoyiannopoulos PG, Zampeli E, Moutsopoulos HM. Autoimmune rheumatic disorders: pathogenetic and laboratory aspects. Immunology and

Rheumatology in Questions. 2021:29-47. doi: 10.1007/978-3-030-56670-8_2

20. Li L, Wei H, Zhang YW, Zhao S, Che G, Wang Y, Chen L. Differential expression of long non-coding RNAs as diagnostic markers for lung cancer and other malignant tumors. Aging (Albany NY). 2021;13(20):23842-23867. doi: 10.18632/aging.203523.
21. Carvajal Alegria G, Gazeau P, Hillion S, Daïen CI, Cornec DYK. Could Lymphocyte Profiling be Useful to Diagnose Systemic Autoimmune Diseases? Clin Rev Allergy Immunol. 2017;53(2):219-236. doi: 10.1007/s12016-017-8608-5.
22. Hysa E, Lercara A, Cere A, Gotelli E, Gerli V, Paolino S, Pizzorni C, Sulli A, Smith V, Cutolo M. Temporomandibular disorders in immune-mediated rheumatic diseases of the adult: a systematic review. InSeminars in Arthritis and Rheumatism 2023; p. 152215. WB Saunders.

Mehmandar-Oskuie A, Jahankhani K, Rostamlou A, Mardafkan N, Karamali N, Razavi ZS, Mardi A. Molecular mechanism of lncRNAs in pathogenesis and diagnosis of auto-immune diseases, with a special focus on lncRNA-based therapeutic approaches. Life Sci. 2024;336:122322. doi: 10.1016/j.lfs.2023.122322.