Type of the Paper (Systemic Review)

Long Non-coding RNA HOTAIR as Diagnostic Marker in Dermatological Autoimmune Diseases: A Systematic Review

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Abstract:
Damage to different organs is caused by aberrant responses from the innate and adaptive immune systems in autoimmune disorders, which encompass a variety of issues. The cause of autoimmune diseases is a very complex and poorly understood phenomenon. The search results contained original research from PubMed, Medline, and EMBASE. There were no review papers included. Studies must have published at least one IncRNA that they discovered through experimentation. Psoriasis, alopecia areata, systemic sclerosis, and melanoma were among the autoimmune dermatological conditions that were mentioned. Except for alopecia areata, where expression was downregulated relative to control, HOTAIR expression was significantly higher in cases of autoimmune dermatological diseases than in the control group in all cases. We can conclude that the long non-coding RNA known as HOTAIR functions as a diagnostic marker for skin autoimmune diseases.

Keywords: autoimmune diseases; HOTAIR; long non-coding RNA.

1. Introduction
Psoriatic arthritis (PsA) is a persistent, immune-mediated, unevenly distributed inflammatory condition affecting the joints. It is typified by inflammation of the synovial membrane and the areas where tendons or ligaments attach to the bone (enthesis), which can ultimately lead to joint erosion and the creation of new bone [1]. Approximately 30% of individuals with skin psoriasis may experience the development
of PsA, with a prevalence rate estimated at 1% in the overall population. Psoriatic arthritis shares clinical and genetic traits with other seronegative spondyloarthritis types [2, 3]. The 2006 Classification Criteria for Psoriatic Arthritis [CASPAR criteria] define PsA, and use it to enroll patients in clinical trials, and support physicians; however, the Psoriatic arthritis diagnostic criteria have not been confirmed [4, 5]. As a result, after ruling out the possibility of other seronegative arthritis, the diagnosis of PsA is primarily based on clinical symptoms. Moreover, no useful diagnostic tests are available at this time.

Although much remains to be understood, autoimmunity and autoinflammation are thought to play major roles in the pathogenesis of PsA. Synovial tissue in PsA is characterized by marked angiogenesis, T-cell infiltration, and synovial hyperplasia along with increased protease and cytokine production. These results might intensify the local inflammatory process, which would lead to joint destruction in the end [6]. One important inflammatory mediator that has been connected to the advancement of joint degeneration in PsA patients is tumor necrosis factor-alpha (TNF-α) [6]. Currently, TNF-α inhibitors are used to treat psoriatic arthritis. However, a considerable fraction of people with PsA show insufficient reaction to TNF-α antagonists [1, 7]. As a result, additional cytokines, such as IL-12, IL-17, and interleukin-23 [IL-23], have become key players for biological agents [1, 7]. IL-17 plays a critical role in the development and course of the illness [8].

LncRNAs are significant molecules involved in inflammatory and immunological processes; they affect gene expression in a variety of ways [11]. There is little evidence that psoriasis causes the deregulation of specific lncRNAs, and no studies have looked at the expression patterns of these lncRNAs in patients with psoriatic arthritis [12, 13].
2. Methods

2.1. Selection criteria for studies

Inclusion criteria

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

Exclusion criteria

Languages other than English, duplicates, non-clinical outcome studies, case report studies, case series studies, review articles, cross-sectional studies, abstract only, not full text, cadaver or Model Studies, and data sets that are considered as duplicated or overlapping.

2.2. Statistical considerations

The results of all relevant research were merged using systematic review management software, ensuring that each study met the established inclusion criteria. A PRISMA [Preferred Reporting Items for Systematic Reviews and Meta-Analyses] flow chart was built to demonstrate the process of selecting papers for review (Figure 1). This chart shows how many studies were included in the review, screened, and appraised for eligibility. Each trial included in the study had its potential for bias assessed using the Cochrane Collaboration's risk-assessment technique. They included elements like as blinding, randomization, and the thoroughness with which outcome reporting was conducted. The relative risk of each primary outcome measure, including the frequency of thromboembolic events and bleeding complications, was calculated. This necessitated merging data from multiple research and using statistical techniques appropriate for meta-analysis, such as random-effects models or fixed-effects models, based on the heterogeneity observed in the studies. \( \hat{p} \) statistics were used to analyze heterogeneity in study results. Sensitivity analyses were conducted to examine how different methodologies and participant characteristics affected the overall results. To determine the impact of unpublished studies on the review's conclusions, publication bias was assessed using techniques such as funnel plots and Egger's regression test.
3. Results

Four studies were included three as Case-control studies and one retrospective. A total of 200 participants were included and divided into case and control groups with a mean age was 43.06 years as shown in Table 1.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Type</th>
<th>Group</th>
<th>Age</th>
<th>Male/Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mohamad et al.</td>
<td>2023</td>
<td>Case-control</td>
<td>Control (50)</td>
<td>Cases (50)</td>
<td>50/50 in case group, 50/50 in control group.</td>
</tr>
<tr>
<td>Zahra et al. [15]</td>
<td>2023</td>
<td>Case-control</td>
<td>Control (20), Cases (40)</td>
<td>Cases (37.8)</td>
<td>Control (41.4)</td>
</tr>
<tr>
<td>Wasson et al.</td>
<td>2020</td>
<td>Case-control</td>
<td>Cases (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cantile et al.</td>
<td>2017</td>
<td>Retrospective</td>
<td>Cases (37)</td>
<td>50</td>
<td>16/21</td>
</tr>
</tbody>
</table>

Autoimmune dermatological disease and HOTAIR expression. Autoimmune dermatological diseases included were psoriasis, alopecia areata, systemic sclerosis and melanoma in all diseases HOTAIR expression was significantly higher in cases with autoimmune dermatological disease than in control except in alopecia areata expression was down-regulated than control as shown in Table 2.

Table 2. Autoimmune dermatological disease and HOTAIR expression.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Disease</th>
<th>HOTAIR expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mohamad et al.</td>
<td>2023</td>
<td>Alopecia areata</td>
<td>• Significantly, AA individuals had a downregulated serum expression of</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>lncRNA HOTAIR ($p &lt; 0.001$).</td>
</tr>
<tr>
<td>Zahra et al.</td>
<td>2023</td>
<td>Psoriasis</td>
<td>• Expression of the HOTAIR in 40 psoriatic patients' serum was assessed in comparison with its level in the serum of 20 matched control subjects. It showed a highly significant statistical result of upregulation in the expression of the</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Disease</td>
<td>Findings</td>
</tr>
<tr>
<td>-----------------------</td>
<td>------</td>
<td>--------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Wasson et al. [16]</td>
<td>2020</td>
<td>Systemic sclerosis</td>
<td>● Dermal fibroblasts overexpressing HOTAIR induced the Hedgehog pathway's transcription factor GLI2 production. The epigenetic suppression of miRNA-34a expression results in the activation of Notch signalling, which facilitates the process. Reduced GLI2 expression was observed in fibroblasts that express HOTAIR and in fibroblasts from patients with systemic sclerosis (SSc) due to suppression of H3K27 methylation and Notch signalling. Crucially, the pro-fibrotic phenotype caused by HOTAIR may be alleviated by inhibiting the action of GLI2 by GANT61 or siRNA.</td>
</tr>
<tr>
<td>Cantile et al. [17]</td>
<td>2017</td>
<td>Melanoma</td>
<td>● In all of the benign melanocytic lesions, HOTAIR was not found. The HOTAIR staining showed a significantly high intensity in all primary tissues and the corresponding metastases, but a significantly low intensity in the primary pT1 lesions. Surprisingly, they found that HOTAIR was present in certain cells inside the tumour, though the amount of positive decreased in lymphocytes located farther away from the tumour. Additionally, HOTAIR was found in the serum of some patients who had metastatic illnesses.</td>
</tr>
</tbody>
</table>
4. Discussion

Autoimmune disorders encompass a diverse range of illnesses that arise from abnormal immune responses to antigens inside the body. These immune reactions result in attacks on healthy molecules, cells, and tissues, leading to damage in many systems and organs of the human body [18].

The term "autoimmune diseases" refers to a broad category of complicated illnesses, the most common of which are RA, SSc, SLE, idiopathic inflammatory myopathy [IIM], and Sjögren's syndrome (pSS). These illnesses can manifest clinically as anything from minor skin rashes to severe organ dysfunction. Most autoimmune conditions are difficult for doctors to diagnose and treat quickly because the pathogenic process involved in these illnesses is complex and still poorly understood. Therefore, it's imperative to identify the key regulators in autoimmune diseases and learn more about the underlying molecular mechanisms [19, 20].

According to Cao et al. (2020), there is a decrease in IncRNA TUG1 in SLE patients' PBMCs, compared to healthy controls [21]. TUG1 levels were even lower in SLE patients with lupus nephritis, according to these authors' findings. Additionally, they found a negative correlation between TUG1 levels and 24-hour urine protein, SLEDAI, ESR, and length of illness. Because of this, this IncRNA may serve as a particular diagnostic marker for people who have systemic lupus erythematosus [SLE] or SLE combined with lupus nephritis. Circulating IncRNAs may be a promising biomarker for SLE, according to mounting evidence. Moreover, it has been discovered that the serum exosomes of RA patients contain IncRNAs. These include TUG1, NEAT1, and MALAT1.

Mohamad et al. (2023) sought to evaluate the relationship between the onset, course, and severity of AA and the levels of miRNA-205, HOTAIR, IncRNA, and TGF-β1 [14]. There were two participant groups, according to the case-control study: fifty people with AA diagnoses and fifty matched healthy controls. Using quantitative RT-PCR, the expression levels of long noncoding RNA HOTAIR and miRNA-205 were determined. Conversely, ELISA methods were employed to ascertain the blood's TGF-β1 levels. It was discovered that AA individuals had considerably lower blood levels of the long noncoding RNA HOTAIR, with a P value of less than 0.001. Moreover, it was demonstrated that these people had noticeably higher blood levels of TGF-β1 and miRNA-205. Karimi et al. (2022) sought to evaluate the role of IncRNAs in both innate and adaptive immune responses,
as well as their irregularity in the development of autoimmune disorders [22]. Their study highlighted the potential involvement of low lncRNA HOTAIR serum expression and high TGF-β1 and miRNA-205 serum expression in the development of AA.

**Conclusion**

Long non-coding RNA HOTAIR can be used as a diagnostic marker for dermatological autoimmune diseases.

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

**References**


