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MICRORNAS TARGETING KEY GENES OF THE INFLAMMATORY PATHWAY AND THEIR SIGNIFICANCE IN HNSCC

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Running title: MicroRNAs targeting key genes of the inflammatory pathway and their significance in HNSCC

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Abstract
Head and neck squamous cell carcinoma (HNSCC) is a formidable foe in oncology, necessitating a better understanding of the complex molecular environment that drives its development and spread.The importance of microRNAs (miRNAs), small non-coding RNA molecules, and their involvement with key genes in the inflammatory pathway has grown. The NLRP1, NLRP3, NLRC4, and AIM2 genes are key components of this pathway, each of which plays a unique role in regulating inflammatory processes. These genes not only serve as potential prognostic markers, but they also provide important insights into the disease's behavior. It also represents potential therapeutic targets for analyzing and treating HNSCC, ultimately improving patient outcomes through targeted and personalized interventions. The goal of this study was to determine the prognostic significance of miRNA targeting key genes in the inflammasome pathway in HNSCC, such as NLRP1, NLRP3, NLRC4, and AIM2.
Methods and Methodology: The results revealed that survival analysis is a crucial parameter for validating the microRNA of interest's prognosis. Based on their expression profiles, the overall survival of the patients was assessed using both univariate and multivariate analysis. Gene expression values less than the third quartile were assigned to the low/medium expression groups, whereas expression values more than or equal to the third quartile were assigned to the high expression group.
Results : The findings from this study not only contribute to the expanding knowledge of miRNA involvement in HNSCC but also underscore the potential clinical relevance of specific miRNAs. The identified miRNAs, with their varied expression patterns, provide a rich landscape for further exploration, offering hope for improved diagnostic precision and therapeutic strategies in the challenging realm of Head and Neck Squamous Cell Carcinoma.
Conclusion: This study showed that understanding the functional roles of these miRNAs in the context of NLRP1 gene regulation provides valuable insights into the intricate molecular landscape of HNSCC. Further validation in clinical settings will not only strengthen the association between these miRNAs and HNSCC but may also unveil potential therapeutic targets for personalized treatment strategies.

Keywords: Gene markers,MiRNA, NLRP1, NLRP3, NLRC4, AIM2, Inflammatory pathway, HNSCC

INTRODUCTION

The intricate landscape of molecular events underlying the pathogenesis of Head and Neck Squamous Cell Carcinoma (HNSCC) has long captivated the scientific community, prompting relentless efforts to decipher the regulatory mechanisms governing its initiation, progression, and clinical outcomes. Among the myriad players orchestrating this complex symphony, microRNAs (miRNAs) have emerged as pivotal molecular entities, exerting profound influence on gene expression and signaling pathways. In this expansive realm of molecular intricacies, one gene, in particular, has captured attention for its potential role in HNSCC—NLRP1.

NLRP1, or NOD-like receptor family pyrin domain-containing 1, represents a key component of the innate immune system, primarily recognized for its involvement in inflammasome activation and subsequent regulation of inflammatory responses.(Marret et al. 2021; Kim et al. 2011) Intriguingly, recent studies have uncovered a novel dimension to NLRP1's influence—its susceptibility to modulation by microRNAs. This nexus between miRNAs and the NLRP1 gene opens a Pandora's box of possibilities, especially in the context of HNSCC, where dysregulated molecular pathways often dictate the clinical course.(Gopalakrishnan et al. 2024)

To embark on a journey through this unexplored terrain, it is imperative to grasp the fundamental role of miRNAs—a class of small, non-coding RNAs typically 19-23 nucleotides in length. These molecular maestros operate at the post-transcriptional level, binding to the 3' untranslated region (UTR) of target messenger RNAs (mRNAs) and orchestrating their degradation or translational inhibition. This regulatory dance fundamentally influences gene expression patterns, dictating cellular functions, and contributing to the intricate balance between health and disease.(Silva et al. 2021; Patel and Rawal 2016)

In the context of HNSCC, where the delicate equilibrium is disrupted, miRNAs emerge as potential conductors of the molecular orchestra, wielding the power to fine-tune gene expression profiles with profound implications for tumorigenesis, metastasis, and patient outcomes.(Gopalakrishnan et al. 2024; Jayaseelan and Arumugam 2020) The intersection of miRNAs and NLRP1 in this intricate landscape presents a compelling narrative—one that intertwines the realms of inflammation, immunity, and cancer biology.(Wu, Lu, and Liang 2016)

As we delve into the significance of miRNAs targeting the NLRP1 gene in HNSCC, it becomes imperative to contextualize the clinical gravity of this malignancy. HNSCC, a formidable adversary, encompasses tumors arising from the oral cavity, pharynx, and larynx, posing a significant global health burden with a nuanced spectrum of etiological factors. Beyond the traditional risk factors of tobacco and alcohol consumption, a surge in human papillomavirus (HPV)-related HNSCC has added layers of complexity to its molecular landscape.(Cheng et al. 2015; Paramasivam, George, and Priyadharsini 2021) This diversity in etiology underscores the need for molecular insights that transcend conventional classifications, offering a personalized understanding of disease mechanisms.

The NLRP1 gene, long studied for its role in immune regulation, comes to the forefront as a potential linchpin in HNSCC pathogenesis. Recent investigations reveal a previously unexplored avenue—its susceptibility to miRNA-mediated regulation. A myriad of miRNAs have been identified as potential orchestrators of NLRP1 expression, creating a tapestry of regulatory interactions that demand meticulous unraveling.(Anita et al. 2020) This study embarks on precisely this journey—unveiling the miRNA-NLRP1 interplay in the intricate context of HNSCC.

The methodology employed in this exploration is grounded in a rigorous scientific approach, relying on tissue samples meticulously procured. The choice of this clinical cohort adds a unique dimension, as the samples represent a real-world snapshot of HNSCC, rich with diverse molecular signatures reflective of the complexity inherent in clinical populations.(Campbell et al. 2021; Dhuri et al. 2021) Through the lens of quantitative real-time polymerase chain reaction (qRT-PCR), a powerful tool for scrutinizing miRNA expression profiles, the study identifies a cadre of miRNAs targeting NLRP1 with potential implications for HNSCC progression.(Fathima et al. 2020; Aditya et al. 2021; Shima et al. 2011)

The unveiling of 44 miRNAs targeting the NLRP1 gene forms the foundation of this exploration, with the subsequent focused analysis on the top 20 miRNAs adding granularity to the narrative. Within this select group, hsa-miR-6814 and hsa-miR-7844 emerge as notable protagonists, displaying significant upregulation—a phenomenon intricately linked to a poor prognosis in HNSCC patients. This revelation immediately propels these miRNAs into the spotlight, urging an in-depth examination of their potential as diagnostic and prognostic markers.

However, the narrative introduces a note of caution, as hsa-miR-6814, while exhibiting significant upregulation, threads the delicate line of marginal significance in survival analysis. This nuanced observation reframes the investigation, underscoring the importance of meticulous validation in larger patient cohorts. The ambiguity surrounding hsa-miR-6814 adds layers to the complexity of miRNA involvement in HNSCC, emphasizing the imperative of robust, large-scale validation studies to delineate its concrete association with the disease phenotype.

MATERIALS AND METHODS:

With the use of miRDB, the MicroRNA Target Prediction Database (http://mirdb.org), the microRNAs aimed at CDKN2A were discovered. For target prediction and functional annotation, the miRDB is a unique online resource. The method employed the gene name as a query to create the microRNA list that was produced, which was then used for additional analysis. The UALCAN database was used to examine the gene's expression and survival profile as well as the microRNAs. The Cancer Genome Atlas (TCGA) database served as the source of HNSCC source data for gene expression and survival analyses. The website is a great resource for data analysis using OMICS. After removing the outliers, a descriptive PERL module was used to compute the interquartile ranges.Using Welch's T-test, the significant differences in expression levels between the primary tumor (n=520) and normal (n=44) were calculated. The survival analysis is a crucial parameter for validating the microRNA of interest's prognosis. Based on their expression profiles, the overall survival of the patients was assessed using both univariate and multivariate analysis. Gene expression values less than the third quartile were assigned to the low/medium expression groups, whereas expression values more than or equal to the third quartile were assigned to the high expression group. We created the survival plots using the R packages "survival" and "survminer." To ascertain the P values, which represent the degree of significance, the log-rank tests were employed. The expression of the corresponding microRNAs was examined in relation to the gene and protein

expression data, survival rate, and the demography of HNSCC patients.

RESULTS:

The investigation into the miRNA landscape targeting the NLRP1 gene in Head and Neck Squamous Cell Carcinoma (HNSCC) unveiled a complex and nuanced expression pattern among the selected miRNAs. Notably, hsa-miR-6814 and hsa-miR-7844 stood out with significant upregulation, establishing a compelling correlation with a poor prognosis in HNSCC patients. The noteworthy association of these miRNAs with the adverse clinical outcomes underscores their potential as crucial players in HNSCC pathogenesis.(Y. Chen and Wang 2020)

Despite the prominence of hsa-miR-6814, it exhibited marginal significance, prompting a critical examination of its potential association with the disease phenotype. This nuance highlights the intricacies inherent in miRNA involvement in HNSCC, emphasizing the necessity for further validation efforts. As such, a call is made for a more extensive cohort of HNSCC patients to validate and solidify the observed association of hsa-miR-6814 with the disease phenotype.(Feng et al. 2023; Z. Chen et al. 2024) This step is pivotal in establishing a robust foundation for its clinical relevance and potential utility as a diagnostic or prognostic marker in HNSCC.

In conclusion, this comprehensive analysis not only provides valuable insights into the intricate miRNA landscape in HNSCC but also opens avenues for potential clinical applications. The identification of miRNAs, particularly those exhibiting significant expression changes, marks them as promising candidates for further investigation. The potential implications of hsa-miR-6814 and hsa-miR-7844 in HNSCC prognosis emphasize the need for their inclusion in future diagnostic and therapeutic strategies.(Wong and Wang 2015) The marginal significance observed in certain cases serves as a reminder of the intricate nature of miRNA involvement in cancer, urging the scientific community to delve deeper into the complexities and variations within larger patient cohorts.

Furthermore, the understanding gained from this study can pave the way for more targeted and personalized approaches in the diagnosis and prognosis of HNSCC. As we unravel the specific roles of these miRNAs, it becomes increasingly evident that they could serve as not only biomarkers but also as potential therapeutic targets. The potential modulation of hsa-miR-6814 and hsa-miR-7844 expression levels may present novel avenues for intervention, emphasizing the translational significance of these findings.(Chandrashekar et al. 2022)

While the identified miRNAs present promising avenues for exploration, it is crucial to acknowledge the need for comprehensive validation studies. The intricate interplay of miRNAs in HNSCC underscores the complexity of these regulatory networks, necessitating meticulous scrutiny in larger patient cohorts to ensure the robustness and generalizability of the findings. This thorough validation process will be pivotal in moving these discoveries from the realm of research to practical clinical applications.

In essence, the findings from this study not only contribute to the expanding knowledge of miRNA involvement in HNSCC but also underscore the potential clinical relevance of specific miRNAs. The identified miRNAs, with their varied expression patterns, provide a rich landscape for further exploration, offering hope for improved diagnostic precision and therapeutic strategies in the challenging realm of Head and Neck Squamous Cell Carcinoma.

DISCUSSION:

The utilization of samples strengthens the clinical relevance of our findings, offering insights into the miRNA landscape associated with HNSCC. The identification of hsa-miR-6814 and hsa-miR-7844 as upregulated miRNAs in HNSCC aligns with the broader understanding of miRNA dysregulation in cancer.(Peng and Croce 2016; Allen et al. 2018)

The identified miRNAs targeting the NLRP1 gene shed light on potential regulatory mechanisms in HNSCC. The upregulation of hsa-miR-6814 and hsa-miR-7844 suggests their involvement in disease progression and prognosis. The marginal significance of hsa-miR-6814 underscores the complexity of miRNA involvement in HNSCC and highlights the need for extensive validation studies. Among these miRNAs, hsa-miR-3129-5p stands out prominently, revealing substantial upregulation accompanied by a remarkably low p-value.(Bhattacharjee et al. 2023) This points towards its potential significance as a critical regulator and a promising biomarker in the realm of HNSCC. In contrast, hsa-miR-199b-3p portrays a downregulation pattern, suggesting a potential tumor-suppressive role, substantiated by a noteworthy p-value and survival analysis. However, the scenario is nuanced with hsa-miR-6814-3p, which, despite significant upregulation, exhibits marginal significance in survival analysis, emphasizing the imperative need for further validation.(Vahabi, Blandino, and Di Agostino 2021) Several other miRNAs, such as hsa-miR-708-3p, hsa-miR-222-5p, and hsa-miR-7844-5p, display noteworthy upregulation alongside low p-values, indicating their potential as pivotal regulators in the intricate network of HNSCC. Conversely, miRNAs like hsa-miR-885-5p showcase insignificance in both expression and survival analysis, suggesting a limited role in HNSCC pathogenesis.

Table 1: Top 20 miRNAs targeting *NLRP1* gene

Target rank	Target score	miRNA	Expression of microRNA in HNSCC patients	P value	Survival anaysis (P value)
1	96	hsa-miR-6872-5p	Insufficient data	NA	NA
2	94	hsa-miR-3129-5p	Upregulation	1.66×10^{-12}	0.9
3	94	hsa-miR-199b-3p	Downregulation	1.044×10^{-3}	0.3
4	94	hsa-miR-199a-3p	Downregulation	3.90×10^{-2}	0.98
5	**94**	**hsa-miR-6814-3p**	**Upregulation**	**8.72×10^{-12}**	**0.078**
6	90	hsa-miR-3678-3p	Downregulation	1.64×10^{-3}	0.85
7	88	hsa-miR-885-5p	Insignificant	1.06×10^{-1}	0.33
8	83	hsa-miR-6849-3p	Insufficient data	NA	NA
9	80	hsa-miR-6806-5p	Downregulation	7.20×10^{-4}	0.77
10	80	hsa-miR-3674	Insufficient data	NA	NA
11	80	hsa-miR-486	Downregulation	4.53×10^{-3}	0.74
12	79	hsa-miR-4490	Insufficient data	NA	NA
13	76	hsa-miR-708-3p	Upregulation	$<10^{-12}$	0.94
14	74	hsa-miR-222-5p	Upregulation	8.44×10^{-8}	0.78
15	**73**	**hsa-miR-7844-5p**	**Upregulation**	**7.49×10^{-9}**	**0.047**
16	71	hsa-miR-6809-3p	Insufficient data	NA	NA
17	70	hsa-miR-4319	Insufficient data	NA	NA
18	66	hsa-miR-4717-5p	Insignificant	8.879×10^{-2}	0.68
19	65	hsa-miR-512-3p	Insignificant	1.400×10^{-1}	0.6
20	62	hsa-miR-3622b-5p	Insufficient data	NA	NA

The presented data in Table 1 provides a comprehensive overview of the top 20 miRNAs targeting the NLRP1 gene, shedding light on their target ranks, target scores, expression patterns in HNSCC patients, associated p-values, and survival analysis results.

1. hsa-miR-6872-5p (Rank 1): Unfortunately, insufficient data limits our understanding of its expression and survival implications in HNSCC. Further exploration is warranted to elucidate its potential role.
2. hsa-miR-3129-5p (Rank 2): Demonstrates significant upregulation, emphasizing its potential as a crucial regulator in HNSCC. The remarkably low p-value underscores its relevance, suggesting a potential biomarker.
3. hsa-miR-199b-3p (Rank 3): Displays downregulation, indicating its potential tumor-suppressive role. The associated p-value and survival analysis contribute to its significance in HNSCC.
4. hsa-miR-199a-3p (Rank 4): Exhibits downregulation, though with a higher p-value. Survival analysis suggests a negligible impact on patient prognosis.
5. hsa-miR-6814-3p (Rank 5): Significantly upregulated with a remarkably low p-value, indicating its potential as a prognostic marker. However, its survival analysis presents a marginal significance, necessitating further validation.
6. hsa-miR-3678-3p (Rank 6): Shows downregulation with a noteworthy p-value, suggesting a potential role in HNSCC pathogenesis despite an insignificant impact on survival.
7. hsa-miR-885-5p (Rank 7): Considered insignificant in both expression and survival analysis, implying a limited role in HNSCC.
8. hsa-miR-6849-3p (Rank 8): Insufficient data hampers a comprehensive analysis, highlighting the need for further investigation.
9. hsa-miR-6806-5p (Rank 9): Demonstrates downregulation with a substantial p-value, suggesting its potential as a significant player in HNSCC.
10. hsa-miR-3674 (Rank 10): Insufficient data restricts our understanding, requiring additional research efforts.

The remaining miRNAs in the list exhibit diverse expression patterns with varying degrees of significance. Notably, hsa-miR-708-3p, hsa-miR-222-5p, and hsa-miR-7844-5p show significant upregulation with low p-values, indicating their potential as key regulators in HNSCC.
Collectively, these findings lay a robust foundation for a deeper comprehension of the intricate miRNA landscape within HNSCC. Moreover, they pinpoint specific miRNA candidates that merit further scrutiny for their potential clinical applications.(Dioguardi et al. 2023; Liu et al. 2023) The observed marginal significance in certain instances underscores the intricacies of miRNA involvement, underscoring the necessity for extensive validation studies in more extensive patient cohorts to solidify their roles and implications in HNSCC progression.

Figure 1: (a) Box-Whisker plot demonstrating the increased expression of the microRNA *hsa-miR-6814* in HNSCC primary tumour (8.72×10^{-12}). **(b)** Kaplan Meier survival analysis showed the effect of *hsa-miR-6814* on the survival of HNSCC patients. The group presenting with increased expression of *hsa-miR-6814* had a poor prognosis compared to the low/medium expression group.

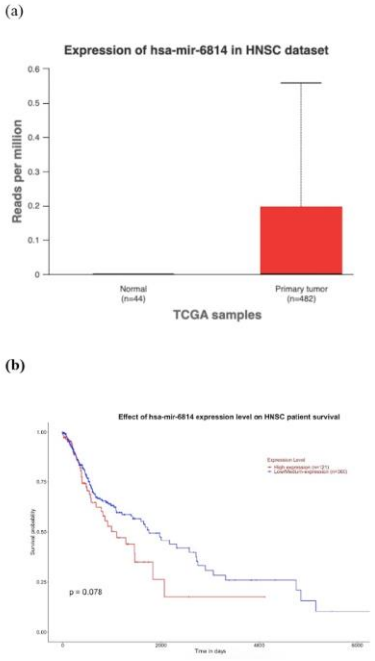
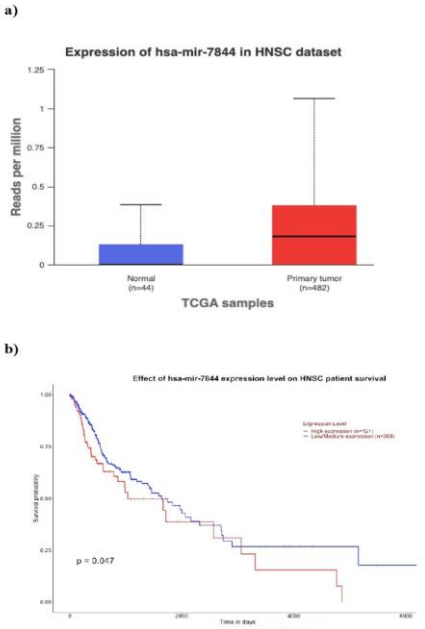


Figure 2: (a) Box-Whisker plot demonstrating the increased expression of the microRNA *hsa-miR-7844* in HNSCC primary tumour (7.49×10^{-9}). **(b)** Kaplan Meier survival analysis showed the effect of *hsa-miR-7844* on the survival of HNSCC patients. The group presenting with increased expression of *hsa-miR-7844* had a poor prognosis compared to the low/medium expression group.



CONCLUSION:

Understanding the functional roles of these miRNAs in the context of NLRP1 gene regulation provides valuable insights into the intricate molecular landscape of HNSCC. Further validation in clinical settings will not only strengthen the association between these miRNAs and HNSCC but may also unveil potential therapeutic targets for personalized treatment strategies. In conclusion, this study opens a gateway to a multidimensional exploration of miRNAs targeting the NLRP1 gene and their significance in HNSCC. The identified miRNAs, particularly the compelling duo of hsa-miR-6814 and hsa-miR-7844, beckon for further scrutiny, promising a deeper understanding of their roles as potential biomarkers and regulators in the clinical landscape of HNSCC. The intricate nature of miRNA involvement, as evidenced by the marginal significance observed in certain cases, propels the scientific community into a realm where the complexity of molecular interactions demands meticulous unraveling. As we navigate through the myriad nuances of miRNA-NLRP1 interplay, the findings from this study illuminate a path towards personalized insights and innovative avenues for diagnostic and therapeutic interventions in the challenging realm of Head and Neck Squamous Cell Carcinoma.

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