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The relationship of human tissue MicroRNAs with those from cerebrospinal fluid, tear, sweat, semen, and saliva

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We previously revealed the relationships of human tissue microRNAs (miRNAs) with those from various body fluids including plasma, bile, urine, serum, and feces, which provided valuable clues for discovering miRNA-based biomarkers for specific diseases. However, it remains unknown for the relationships of human tissue miRNAs with those from other body fluids. Here, by analyzing miRNA expression data from 39 tissue types from healthy humans and various body fluids including cerebrospinal fluid, tear, sweat, semen, and saliva, we have uncovered the relationships of human healthy tissues with those body fluids. All miRNA expression data from body fluids were significantly positively correlated with total expression levels of miRNAs in 39 healthy tissues, and body fluids from different sources exhibited distinct patterns in their relationship with healthy tissues. Moreover, body fluids from different sources showed the highest correlation with different healthy tissues. Notably, saliva samples from patients with oral cavity squamous cell carcinoma showed higher correlations with all tissues than those from healthy controls. These findings together provide evidence for the application of body fluid miRNAs as biomarkers for the diagnosis and treatment of relevant human diseases.

Keywords Body fluids, Tissue, MiRNAs, Bioinformatics

MicroRNAs (miRNAs) are ~ 22-nucleotide-long endogenous non-coding RNAs that regulate a wide range of developmental and cellular processes in eukaryotes, such as developmental timing, cell proliferation, cell death, hematopoiesis, and neurological patterning, by targeting mRNAs for cleavage or translational repression[1–3]. As a result, a growing body of research indicates that miRNAs play critical roles in numerous human diseases, including cancer and autoimmune diseases[4]. Given their significance in human physiology and pathophysiology, miRNAs are considered promising biomarkers for monitoring health and disease states. Furthermore, the presence of miRNAs in diverse human tissues and blood is well established[5,6]. Currently, blood miRNAs are emerging as promising biomarkers for many diseases, such as cancer, cardiovascular diseases, and neurodegenerative diseases[7–9].

Additionally, miRNAs have been consistently detected in various body fluids such as urine, bile, and feces of healthy individuals and patients[10,11]. We previously revealed an overall positive correlation between blood miRNAs and those from other tissues as well as an inverse pattern of their dysregulation in diseases including cancer and inflammation[12]. This finding was further confirmed by Igaz et al.[13]. Moreover, in another study, we demonstrated a positive correlation between miRNAs in body fluids and those in various healthy tissues. In addition, the miRNA profiles in plasma and serum exhibit the closest correlation with those in the pericardium, adipose tissue, liver, and spleen. The miRNAs in urine exhibited the most significant association with those in the kidney. For fecal miRNAs, the strongest relationship was observed with gastrointestinal tissue miRNAs. Furthermore, the miRNA set enrichment analysis revealed that fecal miRNAs with high expression levels are predominantly associated with gastric and colon cancers[14]. These regular patterns among various body fluids and tissues suggested the potential of miRNAs as diagnostic tools, as noted by Jácome et al.[15]. However, the relationship between tissues and other body fluids such as cerebrospinal fluid, tear, sweat, semen, and saliva remains unexplored. Recent investigations have consistently demonstrated the presence of miRNAs in a wide

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range of body fluids derived from both healthy humans and patients, including cerebrospinal fluid, tear, sweat, semen, and saliva[16–20]. Therefore, a more systematic and comprehensive exploration of the relationship between tissue miRNAs and miRNAs from these body fluids will provide valuable clues for the discovery of miRNA-based biomarkers for specific diseases.

In this study, we conducted a bioinformatics analysis of miRNA expression profiles derived from cerebrospinal fluid, tear, sweat, semen, saliva, and various tissues. As a result, we first characterized the relationships among human healthy tissues. Moreover, we observed that miRNAs from body fluids were significantly positively correlated with the total expression levels of miRNAs in 39 healthy tissues and showed specific patterns. Notably, miRNAs from specific body fluids showed distinct patterns with specific tissues, supporting the potential of developing miRNAs from different sources as diagnostic tools for specific diseases.

Materials and methods

MiRNA expression datasets

We obtained the dataset of miRNA expression profiles across 39 healthy human tissues from the study by Liang et al.[21]. Given that we had already analyzed the relationships of tissue miRNAs with those from plasma, serum, urine, bile, and feces, here we did not collect miRNA expression profiles from those body fluids anymore. After a comprehensive review of the GEO database and the literature, we obtained the miRNA expression datasets from body fluids including cerebrospinal fluid, tear, sweat, semen, and saliva, as summarized in **Table 1**. Meanwhile, the averaged miRNA expression profiles in each body fluid from the six studies are available in **Supplementary Table 1**.

Data analysis

We analyzed the miRNA expression data following the strategy described by Cui et al.[14]. We performed Spearman's correlation analysis using R software. To analyze the relationships among healthy tissues, we used multidimensional scaling (MDS), which used (1-Spearman's correlation coefficient) as a distance metric. In addition, given that the placenta is not a general tissue, we excluded it from the 40 healthy tissues. For miRNA functional enrichment analysis, we used the TAM 2.0 tool[22] and focused on the "Function" miRNA set categories. For the TAM analysis, we selected the overlap between the top 1/3 highly or lowly expressed miRNAs in specific body fluids and the 1/3 lowly or highly expressed miRNAs in total tissues as body fluid-upregulated miRNAs and body fluid-downregulated miRNAs, respectively.

Results

The relations among the human healthy tissues

First, we explored the relationships among human healthy tissues based on their miRNA expression profiles. Given that the placenta is not a commonly included tissue, we excluded it and only kept the other 39 tissues for this analysis. We first calculated Spearman's correlation coefficient (Rho) as the similarity metric for each pair of tissues, then used (1-Rho) as the distance metric for each pair. Next, we mapped the 39 tissues into a 2-D Euclidean space using classical multidimensional scaling (MDS) based on their distance matrix.

As shown in **Fig. 1**, the testis and brain are notably distant from other tissues, indicating lower similarity in their miRNA expression profiles compared to other tissues. Notably, both the testis and brain are highly specialized tissues with unique functions. miRNAs in the testis are involved in sperm development[23], while those in the brain are involved in neural differentiation and synapse formation[24,25]; these specific functions may lead to disparities when compared to those of other tissues. Furthermore, the presence of the blood-testis barrier and blood-brain barrier may restrict miRNA exchange[26,27], rendering these two tissues relatively independent and their miRNA expression profiles more distinct.

Moreover, some tissues are clustered together, for example, left atrium, right atrium, pericardium, left ventricle, right ventricle, and heart. Indeed, they all belong to heart. In addition, tissues (jejunum, esophagus, small intestine, proximal colon, colon, duodenum, stomach, ileum, and pancreas) of the digestive system are also closely clustered **(Fig. 1)**. Typically, tissues within a common system originate from the same embryonic layer or developmental pathway[28]. Additionally, miRNAs have been shown to regulate cell differentiation during development[29]. Thus, we hypothesize that their common origin may lead to the retention of similar miRNA expression profiles. From a functional perspective, tissues within a given system are interdependent.

GEO accession	source	publication year	Country	Authors	PMID
GSE121867	Cerebrospinal fluid samples from patients with Intraventricular Hemorrhage and Neural Tube Defects	2018	USA	Kendall Van Keuren-Jensen et al.	30951672
GSE208377	Tears of Kazakh patients with climatic droplet keratopathy and healthy controls	2022	China	Zhixiang Hua et al.	NA
NA	Extracellular vesicle-enriched human sweat collected from volunteers performing rigorous exercise.	2021	Finland	Bart et al.	34103018
GSE176077	Saliva from oral squamous cell carcinoma patients and healthy controls	2023	India	Saproo et al.	36703917
GSE121870	Saliva from gastric cancer patients	2018	USA	David Wong et al.	30951672
GSE49630	Saliva and semen from forensic body	2014	Korea	Park et al.	24915788

Table 1. List of the datasets of MiRNA expression profiles from cerebrospinal fluid, tear, sweat, semen, and saliva.

Fig. 1. **A scatter plot of the relations among the 39 human healthy tissues.** Each point represents one tissue and the Euclidean distance of any two tissues means how they are dis-similar with each other.

For example, the various chambers of the heart are involved in blood circulation and require coordinated physiological activities. miRNAs are involved in regulating common functional pathways, such as myocardial contraction and angiogenesis[30,31], leading to convergent expression patterns.

Body fluids from different sources show specific pattern in their relations with healthy tissues

Globally, all miRNA expression datasets from body fluids show significantly positive correlations with the total expression levels of miRNA profiles across 40 healthy tissues. As shown in **Fig. 2**, the expression levels of miRNAs from cerebrospinal fluid are significantly correlated with total tissue miRNA expression levels (Rho = 0.55, p-value = 4.40e-19, **Fig. 2A**), as are those from tear and saliva (Rho = 0.63, p-value = 3.14e-23, **Fig. 2B**; Rho = 0.61, p-value = 3.84e-22, **Fig. 2D**). In addition, the expression levels of miRNAs from sweat show relatively low but still significant correlations with those of total tissues (Rho = 0.46, p-value = 6.12e-4, **Fig. 2C**). This may be attributable to the primary function of sweat glands being excretion rather than intercellular communication[32], thus rendering miRNA secretion an ancillary function with limited relevance to tissues. Furthermore, the high salt content of sweat may degrade miRNAs[33], thereby reducing their stability.

Remarkably, analysis of a dataset of miRNA expression from saliva and semen in forensic samples[34] reveals that semen also exhibits a positive but weaker correlation with total tissues than saliva (Rho = 0.29, p-value = 4.53e-6 vs. Rho = 0.57, p-value = 9.60e-23). Semen is characterized by a complex composition, which contains various specific cells, including sperm cells and prostate epithelial cells[35,36]; this may result in highly specific miRNAs profiles. In addition, miRNAs in semen are closely related to reproductive system functions[37], thus making them less relevant to tissues than saliva. This indicates that in forensic investigations, when addressing the two core tasks of identification of biological sample sources and inference of donors' physiological health status—a scenario that requires biomarkers to possess multi-tissue association capability—saliva may be more suitable than semen for developing miRNA-based biomarkers in forensic samples[38,39]. Notably, semen miRNAs, due to their close association with reproductive processes such as gamete maturation and embryonic implantation, remain highly valuable biomarkers in the diagnosis of reproductive system diseases[40].

Of note, further analysis of a dataset of miRNA expression from saliva of oral squamous cell carcinoma patients and healthy controls demonstrates that saliva samples from diseased individuals show a higher correlation with total tissues than those from healthy controls (Rho = 0.66, p-value = 3.68e-27 vs. Rho = 0.61, p-value = 3.84e-22). Oral cancer is known to trigger local inflammatory responses and systemic metabolic changes[41]. It has also been demonstrated that cells within the tumor microenvironment actively secrete exosome-containing miRNAs[42], which may enhance communication with other tissues via blood or body fluid circulation[43,44], thereby making the miRNA expression profiles in patients' saliva more similar to those of multiple tissues. This suggests that

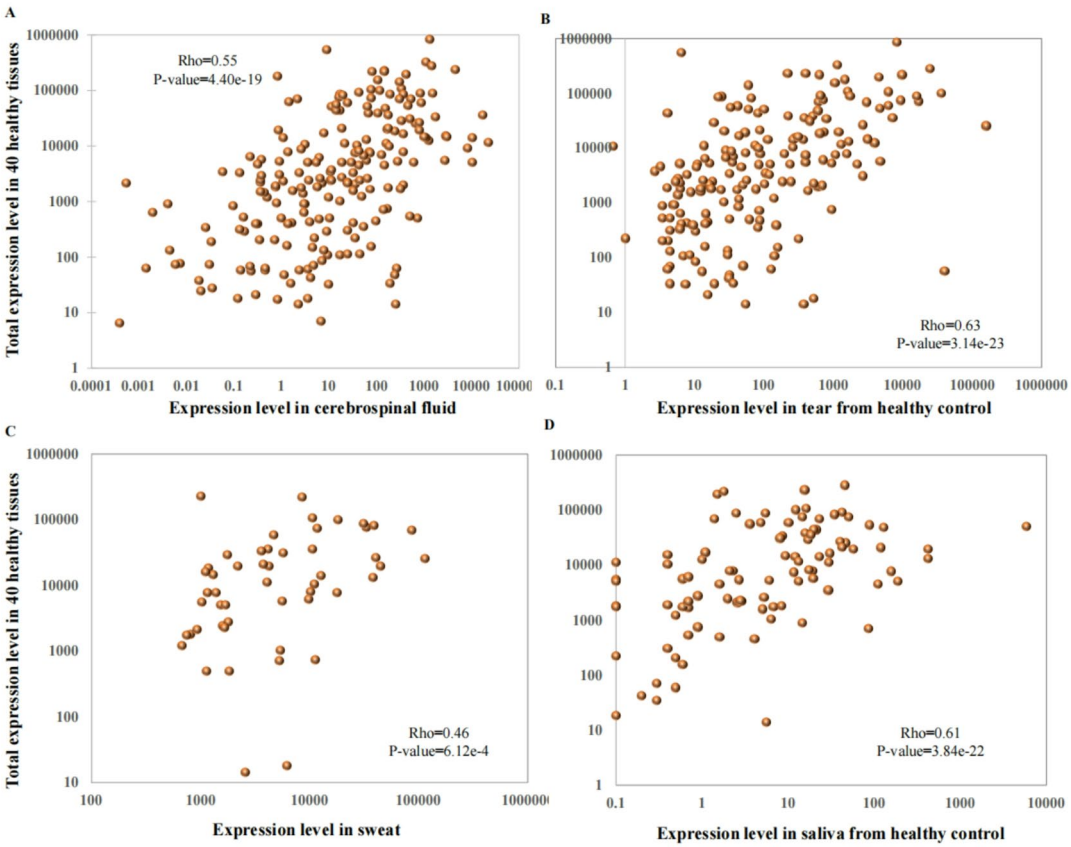

Fig. 2. **The whole relationship between body fluid miRNAs and tissue miRNAs.** **(A)** Correlation of cerebrospinal fluid miRNAs and tissue miRNAs. **(B)** Correlation of tear miRNAs from healthy control and tissue miRNAs. **(C)** Correlation of sweat miRNAs and tissue miRNAs. **(D)** Correlation of saliva miRNAs and tissue miRNAs.

dynamic changes in the strength of body fluid-tissue associations may serve as potential monitoring indicators for disease progression.

Body fluids from different sources show highest correlation with different healthy tissues

Next, we investigated whether different body fluids exhibit distinct correlation patterns with different healthy tissues. For instance, which tissue is most highly correlated with cerebrospinal fluid and other body fluids? As a result, we found that cerebrospinal fluid exhibits the highest correlation with the brain, followed by the spleen, adrenal gland, right atrium, and left atrium, among others **(Fig. 3A)**. Our previous analyses indicated that the miRNA expression profiles in all body fluids may be consistent with those of the tissues they most frequently communicate with[14]. Cerebrospinal fluid, as the extracellular fluid of brain tissue, directly surrounds the central nervous system, thereby facilitating the entry of miRNAs from brain tissue into cerebrospinal fluid via diffusion or active transport[45,46]. In addition, the spleen contributes to the body's immune response via the brain-spleen axis[47], and the adrenal glands maintain physiological homeostasis via the hypothalamic-pituitary-adrenal axis[48]. However, the presence of atrial miRNAs in the circulatory system requires traversal across the blood-brain barrier[49], thereby resulting in a lower correlation.

As a comparison, tear exhibits the highest correlation with the trachea, followed by the stomach, prostate, esophagus, and lung **(Fig. 3B)**. Consistent with the above analysis, sweat exhibits globally low correlations with all tissues but the highest correlations with the trachea, stomach, and pancreas **(Fig. 4A)**. For saliva, interestingly, samples from oral squamous cell carcinoma patients exhibit higher correlations with all tissues than those from healthy controls **(Fig. 4B)**. Additionally, the lung, trachea, esophagus, thymus, and stomach are the top 5 tissues exhibiting the highest correlation with saliva. In addition, saliva from both forensic samples and gastric cancer patients demonstrates a similar pattern (**Supplementary Figs. 1–2**).

We observed that tear, sweat, and saliva have a high degree of association with the trachea and stomach. Saliva is connected to the trachea and stomach via the pharynx and esophagus, and tear communicate with the nasal cavity via the nasolacrimal duct, which connects to the trachea. This anatomical continuity provides a foundation for local microenvironmental exchange. It is also notable that the trachea and stomach are part of the mucosal immune system[50], while tear, saliva, and sweat all participate in the peripheral regulation of mucosal immunity[51–53]. This may provide a theoretical basis for their high correlation with these systems.

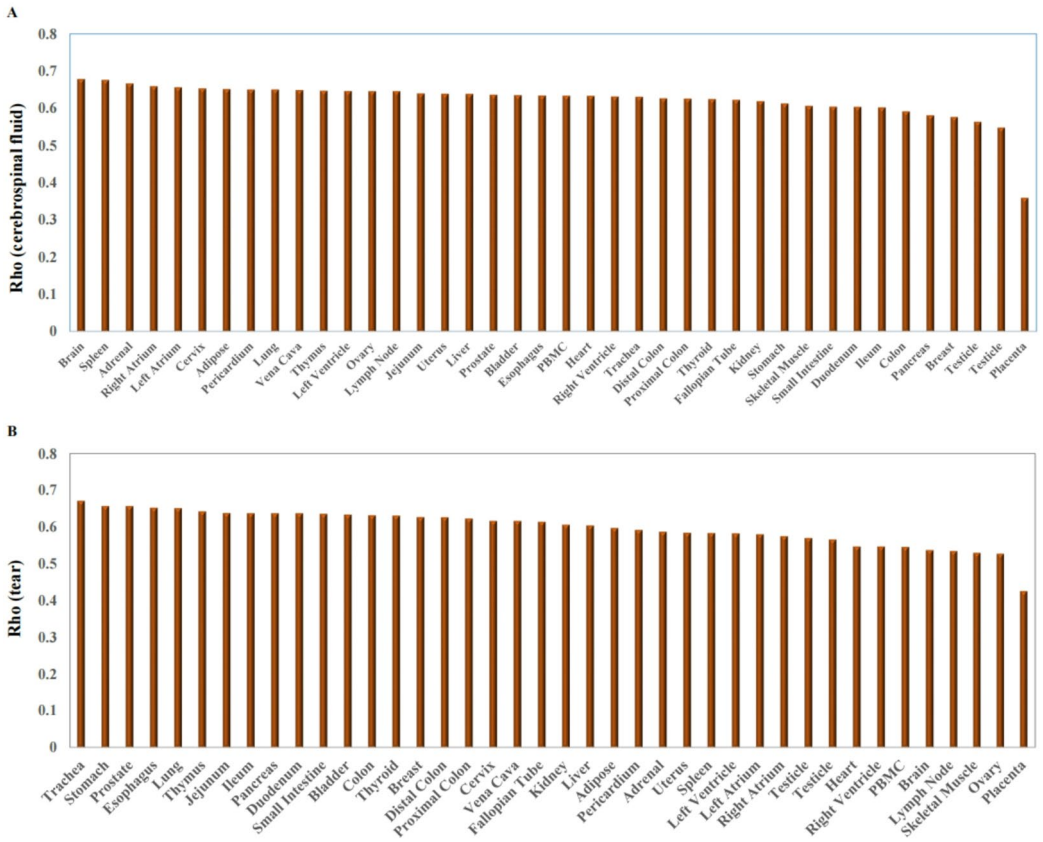

Fig. 3. **Analysis the relationship of body fluid miRNAs with miRNAs in 40 tissues.** (**A**) Correlations between cerebrospinal fluid miRNAs with those in the 40 tissues. (**B**) Correlations between tear miRNAs with those in the 40 tissues.

Highly expressed MiRNAs in specific body fluids are enriched in specific functions

Next, we further investigated the enriched functions of body fluid-upregulated and downregulated miRNAs. Using the TAM tool (see Methods), we first identified the enriched functions of upregulated and downregulated miRNAs in cerebrospinal fluid. The results showed that cerebrospinal fluid-upregulated miRNAs are most enriched in functions such as response to hypoxia, autophagy, and apoptosis **(Fig. 5A)**; whereas downregulated ones are significantly enriched in functions like cell differentiation, cell adhesion, and inflammation among others **(Fig. 5B)**. Using the same approach, we further identified the enriched functions of upregulated and downregulated miRNAs in tear, sweat, and saliva (**Supplementary Table 2**). Because the number of sweat miRNAs is relatively small, there is only 1 upregulated miRNA and 2 downregulated miRNAs. Thus, we performed functional enrichment analysis using these 3 dysregulated miRNAs collectively. For saliva, we identified dysregulated miRNAs by comparing saliva miRNAs from healthy individuals with those from the 39 healthy tissues.

Discussion and conclusion

In conclusion, based on miRNA expression profiles in 39 tissues (excluding the placenta), we characterized the relationships among healthy human tissues and between these tissues and several body fluids, including cerebrospinal fluid, tear, sweat, semen, and saliva. Our findings further demonstrate that body fluids from diverse sources exhibit distinct patterns of association with healthy tissues and the highest correlations with specific tissues. In this study, each body fluid's miRNA profile is compared with the global miRNA expression of 39 types of healthy tissues. This upstream analytical step can establish a baseline for global associations, confirm whether significant correlations exist between body fluids and tissues, and lend biological plausibility to subsequent findings. Furthermore, it can quantify differences in the breadth of tissue associations across different body fluids, clarify the ability of each body fluid to reflect the status of systemic tissues, and additionally provide a reference for analyzing pathological conditions.

Our findings indicate that the testis and brain exhibit distinct characteristics compared to most other tissues, consistent with the conclusions reported by Linsen et al.[54], who analyzed miRNA expression profiles in six rat tissues and found that the brain contained the highest number of tissue-specific miRNAs, followed by the testis. As noted in our previous research[14], a significant positive correlation was identified between miRNAs from plasma, serum, and urine and those from human tissues. A similar relationship was observed for cerebrospinal fluid, saliva, tear, and sweat. A recent study revealed a significant correlation between miRNA expression patterns

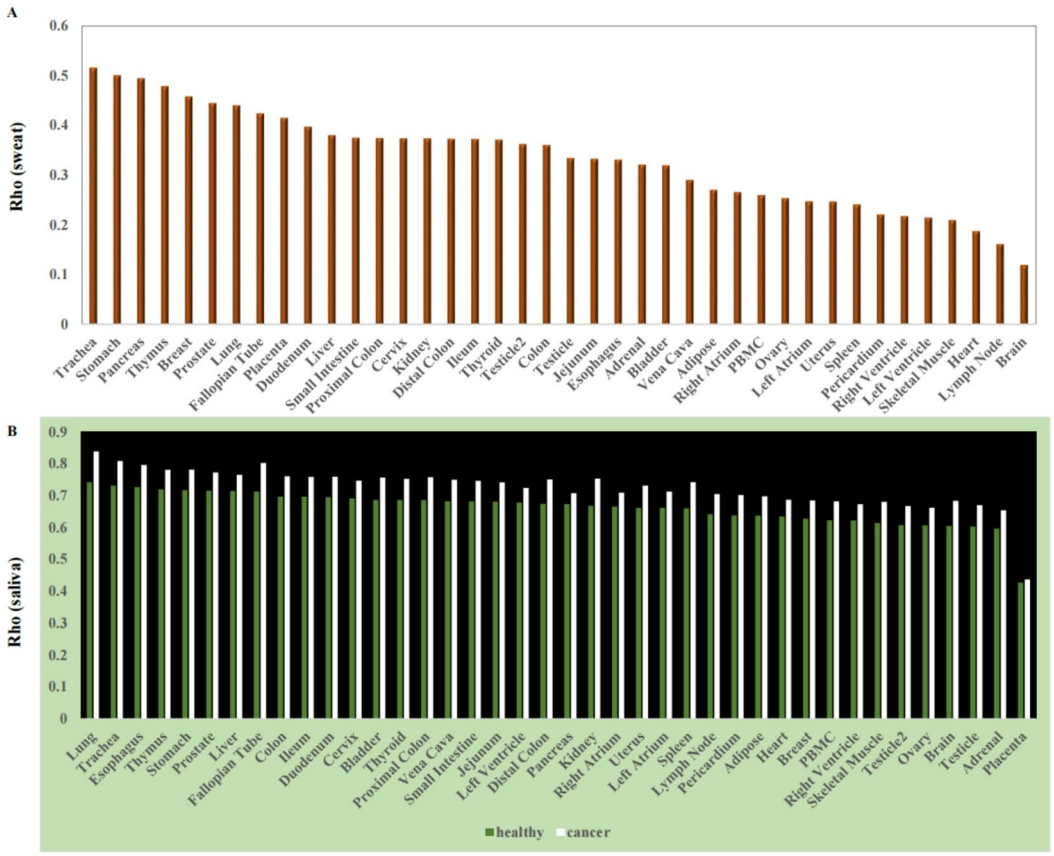

Fig. 4. Analysis the relationship of body fluid miRNAs with miRNAs in 40 tissues. (**A**) Correlations between sweat miRNAs with those in the 40 tissues. (**B**) Correlations between saliva miRNAs from healthy controls and oral squamous cell carcinoma patients with those in the 40 tissues.

in saliva and oral tumor tissues[20]. Specifically, it highlighted parallel expression patterns of miR-7-5p and miR-486-3p in these two biological samples. Together with six other miRNAs, these two miRNAs achieved an area under the curve (AUC) of 0.954 in identifying oral cancer. For tear, research revealed that inhibition of miR-203 enhanced the viability of corneal epithelial cells[55], thereby contributing to the regulation of corneal epithelial homeostasis. This finding demonstrates close communication between tear and ocular tissues. Furthermore, Karvinen et al.[18] provided evidence that levels of miRNAs—specifically miR-21 and miR-26—in sweat can be influenced by endurance exercise intensity. We conclude that miRNA expression levels in sweat may reflect metabolic changes or stress responses in the musculoskeletal system. Overall, there is significant crosstalk between miRNAs in human body fluids and those in tissues.

Our findings further demonstrate that body fluids from diverse sources exhibit the strongest correlations with specific healthy tissues—for example, cerebrospinal fluid, which exhibits a particularly strong correlation with the brain. In the context of brain tumors, cerebrospinal fluid is an optimal source of miRNAs, as it acquires these molecules through direct contact with tumor tissue[56]. Plasma is also regarded as a promising candidate; however, its reliability is limited by the blood-brain barrier. A study revealed that cerebrospinal fluid levels of miR-21 have a sensitivity of 87% and specificity of 93% for differentiating between glioblastoma patients and non-tumor controls[57]. Furthermore, in patients with Alzheimer's disease, lower cerebrospinal fluid levels of miR-451a have been associated with higher cognitive assessment scores and lower depression scale scores[58]. In summary, miRNAs in cerebrospinal fluid offer a promising avenue for assessing brain health and diagnosing neurological diseases.

These findings could guide the development of miRNA-based biomarkers derived from these body fluids. Together, miRNAs play critical roles in mediating communication between human tissues and between body fluids and tissues, and exhibit specific expression patterns in different body fluids and pathological states. Thus, as important mediators of communication between body fluids and tissues, miRNAs may serve as potential candidates for investigating pathogenesis and for diagnosing and treating diseases. Nevertheless, several key questions remain to be answered in future studies. First, the mechanisms underlying the specific association patterns between body fluids from different sources and healthy tissues remain unclear. Second, whether there is a potential correlation in miRNA expression between different body fluids remains unclear. Finally, the reasons for differences in the correlations between body fluids and tissues—when comparing pathological states with healthy controls—remain unclear. Therefore, future studies should collect more extensive datasets for further

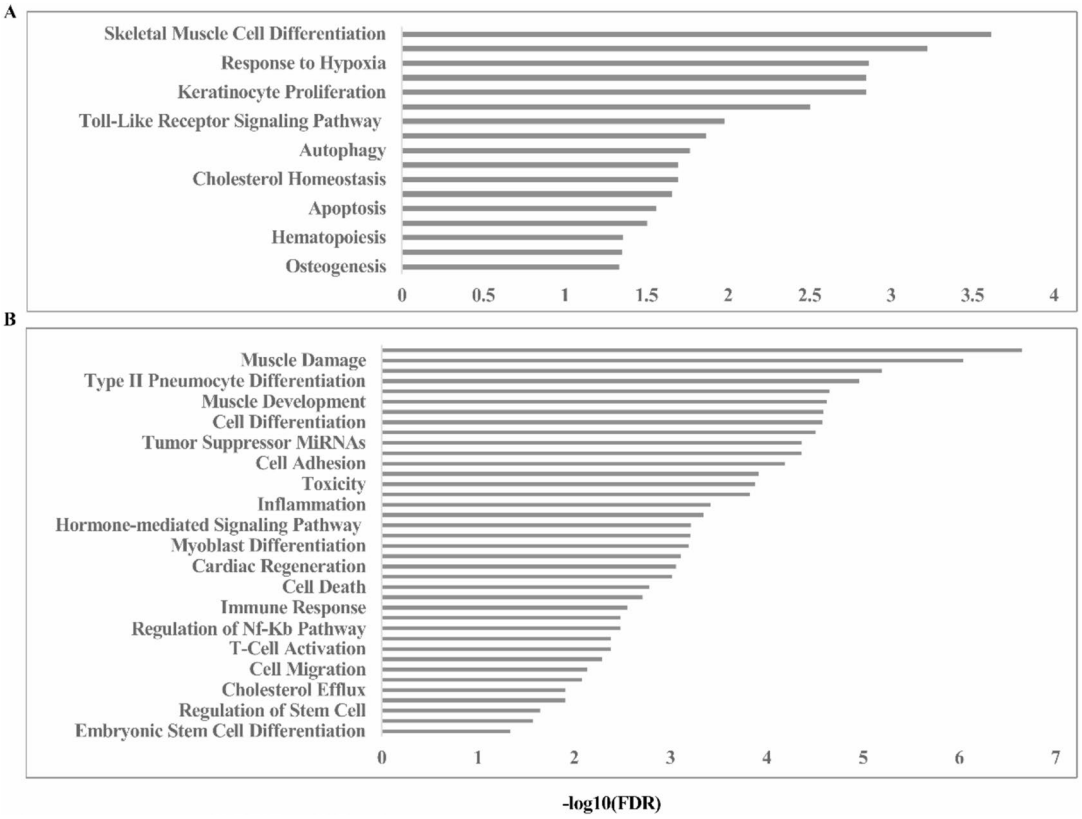

Fig. 5. **Results of the functional enrichment analysis of the** (**A**) up-regulated miRNAs and (**B**) down-regulated miRNAs in cerebrospinal fluid compared to the 39 human healthy tissues.

analysis. Additionally, it would be important to dissect the top miRNAs that have the greatest discriminatory power between body fluids and their most significantly associated tissue of origin, as analyzed by Grasedieck et al.[59]. As the correlation coefficients of miRNA profiles between body fluids and tissues are not sufficiently varied, there seem to be no such miRNAs that can discriminate the most associated tissue from other tissues. However, in some diseased conditions, this type of analysis may help explore this issue.

Data availability

The raw data used in our study are from the publications[21].All data generated or analyzed during this study are available from the corresponding author on reasonable request.

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Author contributions

Q.F., and H.Y. performed the analysis. T.L. took part in the study. S.C. and Q.C. supervised the study. Q.F. and Q.C. wrote the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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