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Research Paper – Araştırma Makalesi

A COMPUTER-BASED STUDY ON BRAIN-HEART AXIS: MIR-423-5P IN HEART FAILURE

BEYİN-KALP EKSENİ ÜZERİNE BİLGİSAYAR TABANLI BIR ÇALIŞMA: KALP YETMEZLİĞİNDE miR-423-5p

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Özet

Kalp yetmezliği (KY), yüksek mortalite ve morbidite oranlarına sahip çoklu organ ve sistemleri etkileyen kompleks bir klinik sendromdur. Son yıllarda kalp ve beyin arasındaki çift yönlü iletişimi tanımlayan kalp-beyin ekseni (KBA), KY'nin patofizyolojisinin anlaşılmasında önemli bir kavram olarak öne çıkmıştır. Bu eksen kapsamında dolaşımdaki mikroRNA'ların (miRNA), organlar arası moleküler sinyal iletiminde rol oynayabileceği düşünülmektedir. Bu çalışmanın amacı, KY'de değiştiği bildirilen miRNA'lar arasından miR-423-5p'yi odak miRNA olarak belirlenmesi, KBA ile ilişkili olası moleküler mekanizmaları bilgisayar tabanlı yöntemlerle araştırmayı amaçlamıştır. Bu amaç doğrultusunda insan kan, serum veya plazma örneklerinden elde edilen literatür verileri dahil edilme kriterleri göz önüne alınarak incelenmiş elde edilen miRNA'lar ortaya koyulmuştur. Bu miRNA'ların beyinde ekspresyonları ve bağımsız çalışmada tutarlı biçimde değişimi incelenmiştir. Bu doğrultuda miR-423-5p potensiyel aday olarak belirlenmişr ve miR-423-5p'nin hedef genleri miRDB, TargetScan, miRWalk ve DIANA-microT veritabanları kullanılarak tahmin edilmiştir. Bu dört veritabanında ortak olarak yer alan 75 adet yüksek güvenilir hedef gen, analize dahil edilerek fonksiyonel zenginleştirme ve protein–protein etkileşim analizleri Metascape platformu aracılığıyla gerçekleştirilmiştir. Analiz sonuçları, miR-423-5p hedef genlerinin hücre içi sinyal iletimi, protein fosforilasyonu ve nöronal süreçlerle ilişkili biyolojik yolaklarda yoğunlaştığını göstermiştir. Ayrıca PRKACA, bu ağın merkezinde yer alan başlıca hub protein olarak tanımlanmıştır. Sonuç olarak bu çalışma, miR-423-5p'nin KY'de KBA ile ilişkili moleküler ağlarda potansiyel bir düzenleyici rol oynayabileceğini göstermek olup ve gelecekte yapılacak deneysel çalışmalar için hipotez oluşturucu bir temel sunmaktadır.

Anahtar Kelimeler: Kalp Yetmezliği, miRNA, Beyin

Abstract

Heart failure (HF) is a complex clinical syndrome affecting multiple organs and systems with high mortality and morbidity rates. In recent years, the heart-brain axis (HBA), that identifed as the dual communication between the heart and brain, has emerged as a crucial concept in understanding the pathophysiology of HF. Within the axis, circulating microRNAs (miRNAs) are thought to play a role in inter-organ molecular signaling. The aim of this study was to identify miR-423-5p as a focal miRNA among those reported to be altered in HF and to investigate possible molecular mechanisms associated with HBA in silico approaches. For the aim, literature data obtained from human blood, serum, or plasma samples were examined, considering the inclusion criteria, and the identified miRNAs were determined. The expression of these miRNAs in the brain and their consistent alteration in independent studies were investigated. Accordingly, miR-423-5p was recognized as a potential candidate, and its target genes were predicted using the miRDB, TargetScan, miRWalk, and DIANA-microT databases. A total of 75 highly reliable target genes from these four databases were included in the analysis, and functional enrichment and protein-protein interaction analyses were performed via the Metascape platform. The analysis results showed that miR-423-5p target genes are concentrated in biological pathways related to intracellular signal transduction, protein phosphorylation, and neuronal processes. Moreover, PRKACA was identified as the main hub protein at the center of the network. In conclusion, this study demonstrates that miR-423-5p may play a potential regulatory role in HBA-related molecular networks in HF and provides a hypothesis-forming basis for future experimental studies.

Keywords: Heart Failure, miRNA, Brain

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1. INTRODUCTION

Heart failure (HF) is a condition of inadequate blood supply in the body due to insufficient heart activity. It leads to major problems that result in high rates of mortality and morbidity (1) It is estimated that approximately 1-2% of the population has this condition and the number increases day by day (2). Although increased life expectancy and developed healthcare techniques bring long and high-quality life, not only HF but also its comorbidities remain a burden. HF alters the body physiology, which leads to several morbidities that include various organs and systems. It is reported that various interactions of signaling in the Heart-Brain Axis (HBA) contribute to the HF progression. Furthermore, the bidirectional pathway could induce cerebral damage following the HF (2,3). Due to this reason, it is crucial to evaluate the central nervous system after HF.

The heart-brain axis (HBA), an outcome of a new insight into physiology, is a connection between two main systems of the body, leading to dual communication. HBA is a complex network; numerous studies have sought to explain the molecular aspects of HBA. Based on them, it controls lots of pathways, including hormones, the autonomic nervous system, cytokines, and miRNAs storage in extracellular vesicles (4). The collaboration between the brain and heart explains pathophysiological alterations that have been known for ages. While most of the brain pathologies cause cardiac problems, including hypertension, congestive heart failure, and atrial fibrillation, on another view, it is known that cardiac impairment results in neurological complications (5-8). Therefore, when a disease originating from either neurological or cardiological cause occurs, other systems involved in the axis should also be examined for prevention or management.

microRNAs (miRNAs) have roles in modulation, variability, and interactivity of functions. miRNAs are a type of RNA including 19-22 nucleotides. Although their effects explained lots of mechanisms until today, it is predicted that what's seen is only the tip of the iceberg, so it is no surprise that miRNAs have a role in HBA. Moreover, growing evidence indicates that heart-derived miRNAs found in the brain (9–11). Given the focus on circulating miRNAs as biomarkers, their potential roles within HBA require a new perspective (2) Therefore, the aim of this study is to investigate the possible pathways of miRNAs after HF, and the regions they are likely to affect, to provide an integrative computer-based approach.

2. METHODS

2.1. miRNA Determination

The study was conducted in silico, so it was not included in the biological sample. Data was gathered in the current literature based on human studies that analysis blood, serum or plasma samples. The inclusion criteria were (1) Human studies, (2) miRNA analysis was done in both control (CTR) and heart failure (HF) groups, and (3) miRNA levels were analyzed from blood, serum, or plasma. Due to the criteria, other species and post-mortem or transplantation tissue analyses were excluded from the research. Among the miRNAs that were altered in HF, expression in the brain tissue was controlled by miRNATissueAtlas (12). Based on these, determined miRNA was utilised in other analyses.

2.2. Determination of miRNA-423-5p Target Genes

To achieve the target genes of miRNA-423-5p, the miRNA-423-5p that was elevated in HF groups, miRDB, TargetScan, mirWalk, and Diana databases were used in analysis (13–16). Predicted miRNA-423-5p targets were filtered to include only genes present in all databases. The total of 75 genes was included in the analysis.

2.3. Functional and Protein-Protein Interaction Enrichment Analysis

Functional enrichment analysis was performed using Metascape, an integrative platform for pathway enrichment and gene annotation. Gene Ontology (GO) enrichment analyses were conducted using the Metascape platform. Enrichment results were corrected for multiple testing, and terms with a false discovery rate (FDR) < 0.05 were considered statistically significant.

For protein–protein interaction analysis, the same gene set was analyzed using the STRING database integrated within Metascape, with the interaction confidence score set to high stringency. The resulting hub gene was determined, and the network was visualized (17).

3. RESULTS

3.1. HBA-Related miRNA Prediction

Based on the literature included, it is shown that there was a significant alteration in the total of 84 miRNAs in the blood/plasma or serum of patients with HF (Table 1). Among them, miRNA-423-5p was the most abundant and expressed in the brain, so miRNA-423-5p was used in the analysis.

Table 1. miRNA determination studies in HBA.

Group	N	Sex (m/f)	Age (years)	Sample Source	Dysregulated miRNAs	References
HF	54	ND	54 ± 7	Plasma	miR-150-5p, miR-26a-5p	(18)
CTR	15	ND	60 ± 12	Plasma		
HF	30	26/18	64.5 ± 9.3	Serum	miR-423-5p, miR-320a, miR-22, miR-92b	(19)
CTR	30	21/19	63 ± 12.2	Serum		
HF	43	32/11	57 ± 12	Plasma	miR-92b-5p	(20)
CTR	34	23/11	62 ± 2	Plasma		
HF	62	42/20	62 ± 8.89	Plasma	miR-21-5p, miR-30a-3p, miR-30a-5p, miR-155-5p, miR-216a, miR-217	(21)
CTR	62	40/42	60 ± 11.80	Plasma		
HF	81	46/35	81.3±6.8	Plasma	miR-499-5p, miR-423-5p, miR-133a, miR-21	(22)
CTR	99	54/45	79.5±5.4	Plasma		

HF	12	12/0	72±3.0	Plasma	miR-423-5p, miR-18b miR-129–5p, miR-1254, miR-675 mir-202, miR622	(23)
CTR	12	12/0	57±1.5	Plasma		
HF	60	ND	64.73 ± 8.18	Blood	miR-1233, miR-183-3p, miR-190a, miR-193b-5p, miR-125a-5p, miR-211–5p, miR-494, miR-545–5p, miR-550a-5p, miR-638, miR-671-5p, miR-193b-3p,	(24)
CTR	30	ND	65.93 ± 6.72	Blood		
HF	42	30/12	56.57 ± 10.35	Serum	miR-30d, miR-502-5p, miR-299-3p, miR-21, miR-650, miR-744, miR-516-5p, miR-182, miR-568, miR-1228, miR-583, miR-595, miR-663b, miR-1296, miR-1825, miR-662 miR-122, miR-3148, miR-518e, miR-129-3p, miR-3155, miR-3175, miR-200a, miR-1979, miR-371-3p, miR-155, miR-1292,	(25)
CTR	15	8/7	51.78±3.9	Serum		
HF	42	31/11	23.62±8.82	Blood	miR-125a-5p, miR-150-5p	(26)
CTR	32	20/12	22.75±9.97	Blood		
HF	28	14/14	69±12	Serum	miR-30b-5pmiR-107, miR-139-5p, miR-150-5p, , miR-335-5p, miR-125a-5p, miR-342-3plet-7a-5p,	(1)
CTR	16	10/6	67±8	Serum		
HF	53	44/9	60±16	Blood	miR-622, miR-519e, miR-520d-5p, miR-1231, miR200b, miR-1228, miR-551b, miR-345, miR-let-7g, miR-558, miR-122,	(27)
CTR	39	23/16	63±13	Blood		
HF	45	25/20	60.8±12.2	Plasma	miR-199a, miR-660-3p, miR-665, miR-1285-3p, miR-4491, miR-206, miR-1268b, miR-130-3p, miR-330-3p, miR-4288miR-221-30, miR-487b-3p,	(28)
CTR	45	24/21	57.7±9.2	Plasma		

3.2. Functional and Protein-Protein Interaction Enrichment Analysis

The examination of 75 genes across all five databases associated with miRNA-423-5p resulted in the clustering of the biological processes to which these genes are affiliated. The analytical results, with each cluster represented in an individual color, are presented in Figures

1 and 2. The hub protein of miRNA-423-5p is found to be Protein Kinase CAMP-Activated Catalytic (PRKACA).

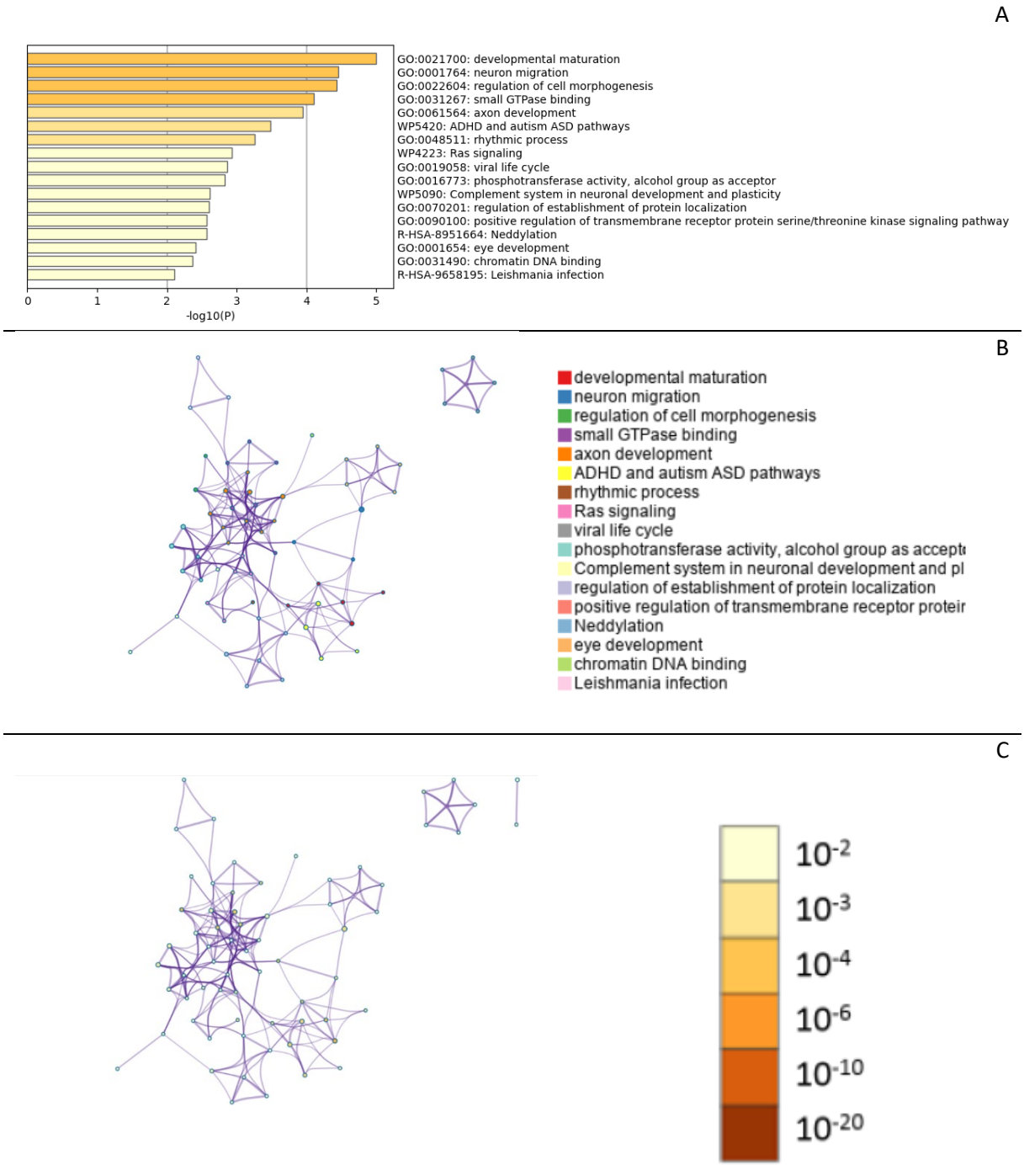

Figure 1: (A) Heatmap for selected GO (B) Network colorod by cluster and (C) Network colorod by P value (Figures obtained from Metascape).

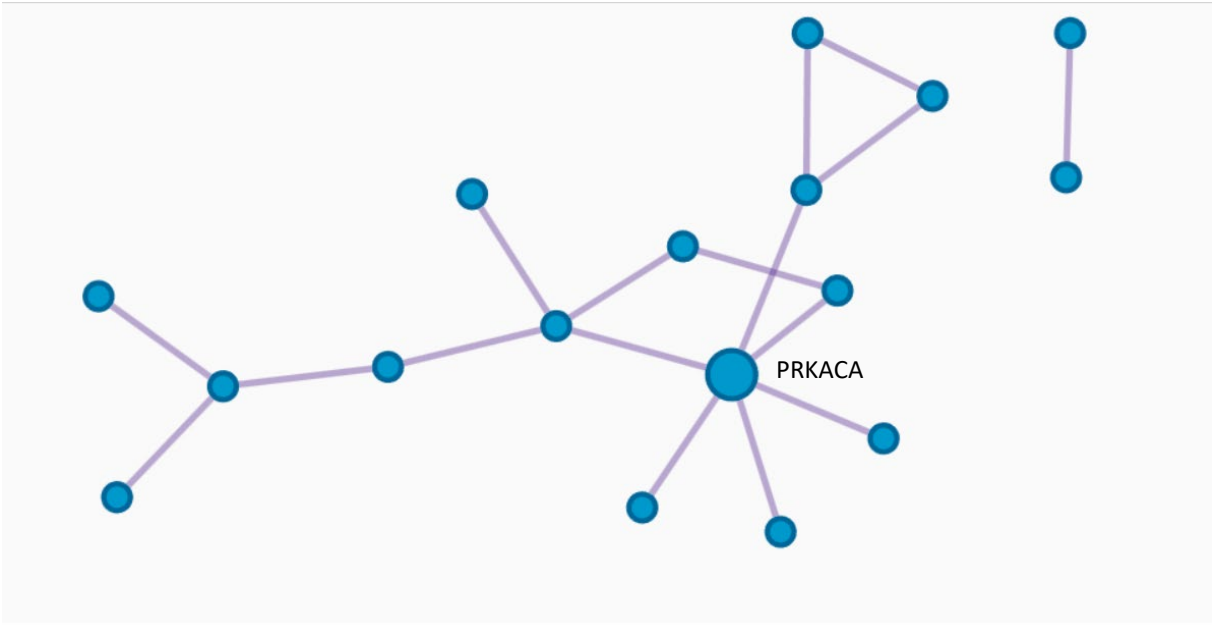

Figure 2: Protein-protein interaction enrichment analysis result (PRKACA: Protein Kinase CAMP-Activated Catalytic)

4. DISCUSSION

In this study, molecular mechanisms that may be associated with HBA in the context of HF were investigated using in silico approaches via circulating miRNAs. Based on the literature, it is revealed that 84 miRNAs have been reported to be statistically significantly altered in blood, serum, or plasma samples from patients diagnosed with HF. Among these miRNAs, miR-423-5p was selected as the focus miRNA due to its consistent increase in multiple independent studies (19,22,23). Therefore, the genes affected by miR-423-5p were examined using databases. Our study showed that miR-423-5p induces neuronal migration and axonal development. Furthermore, PRKACA was identified as the hub gene of this miRNA.

miR-423-5p is a popular miRNA due to its suppressor effects on tumors (29). Moreover, it is exhibited that the miRNA related to the central nervous system in different pathogeneses. However, a controversy exists about whether it is protective or harmful for neurons (30–32). It is reported that the level of miRNA-423-5p was higher than that of healthy controls, compared to the HF (19). Although the opposition, it is revealed that miRNA-423-5p is related to neuron migration, axon development, and developmental maturation in the GO analysis in this study. Thus, miRNA-423-5p effects on the neuronal tissue should be investigated further in expanded studies.

PRKACA is a catalytic subunit and has a critical role in the signal of cAMP (33). It is reported that PRKACA activates the cAMP-BDNF signaling axis, which contributes to synaptic plasticity that restores the brain impairment (34). In this study, it is determined that the potential hub protein of miR-423-5p is PRKACA. Collecting the information, it could be

speculated that rising miR-423-5p could be a protective signal in HBA against the reduction of blood supply.

The study has some limitations, as the results are based entirely on in silico analyses. The lack of experimental validation studies (in vitro or in vivo) limits the ability to definitively establish the functional-level relationship between miR-423-5p and PRKACA. However, the rigorous target selection criteria and multiple analysis approach used demonstrate that the results are biologically significant and conducive to hypothesis generation.

In conclusion, the study provides the potential role of miR-423-5p in BHA-related molecular networks in HF. Future experimental and clinical studies are expected to elucidate the functional effects and therapeutic potential of miR-423-5p along the axis.

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