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The Potential Role of MicroRNAs in Cardiac Myxoma: A comprehensive Review on the Current Evidence

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ABSTRACT

Cardiac myxoma (CM) is the most common primary cardiac tumor, often benign but potentially life-threatening due to embolic events and intra-cardiac obstruction. Recent advances suggest a significant role for microRNAs (miRNAs) in CM pathogenesis, diagnosis, and treatment. This review aims to synthesize current evidence regarding the diagnostic implications of miRNAs in cardiac myxoma. Several miRNAs, including miR-217, miR-218, miR-335, miR-320a, miR-122, and miR-634, have been implicated in regulating proliferation, apoptosis, inflammation, and differentiation in CM. Notably, miR-217 and miR-218 act as tumor suppressors, while dysregulated pathways involving Myocyte Enhancer Factor 2D (MEF2D) and Interleukin-6 (IL-6) further elucidate the molecular basis of tumor progression. Circulating miRNA profiles also offer potential as non-invasive diagnostic biomarkers. miRNAs offer promising avenues for both early detection and targeted therapy in cardiac myxoma. Further research into miRNA-based diagnostics and therapeutics may enhance personalized treatment and reduce recurrence risk in affected patients.

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Introduction

Cardiac masses represent a diverse group of lesions that can be broadly classified into two categories: neoplastic and non-neoplastic. Non-neoplastic masses include vegetations, thrombi, calcifications, and other rare structural abnormalities. In contrast, neoplastic lesions encompass both benign and malignant tumors, originating either within the heart or from metastatic spread, as well as tumors located in the intracardiac or pericardial regions (1-3). These masses are clinically significant due to their potential to impair hemodynamic stability, often through mechanisms such as flow obstruction, embolic events, or disruptions to the heart's electrical or mechanical functions (4, 5). Although primary cardiac tumors are infrequent, autopsy studies estimate their incidence to be between 0.0017% and 0.3%, with prevalence rates ranging from 0.001% to 0.03% (6, 7). In 2015, the World Health Organization (WHO) revised its classification system for cardiac neoplasms, grouping them into benign tumors and tumor-like lesions,

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tumors with uncertain biological potential, germ cell tumors, malignant neoplasms, and pericardial tumors (8). Benign primary cardiac tumors are significantly more prevalent than malignant ones, comprising approximately 75–90% of cases (9, 10). Notably, in its 2021 update, the WHO identified papillary fibroelastoma (PFE) as the most frequently occurring benign cardiac tumor, revising earlier conceptions about tumor prevalence (9,11).

Cardiac myxoma (CM) derives its name from the abundant myxoid extracellular matrix it contains, which is rich in glycoproteins and proteoglycans, interspersed with polygonal cells. This tumor is believed to originate from primitive mesenchymal cells with the potential to differentiate into endothelial cells (12-14). While CM can present at any age, it is more commonly diagnosed in females than males (15). Cardiac myxomas can occur across all age groups, but they most commonly present between the third and sixth decades of life, with an average age of diagnosis around 50 years. There is a slight female predominance, with a female-to-male ratio of approximately 2:1 (6). Most cardiac myxomas arise sporadically and are isolated cases, while only 5–10% show familial inheritance patterns. These tumors typically develop in the atria, with about 75% originating from the left atrium and 18% from the right atrium. In younger patients, especially those without gender bias, cardiac myxomas have been reported as part of genetic syndromes such as Carney complex, often appearing around the age of 20 (16,17).

Early diagnosis and treatment of CM are essential due to the high risk of severe complications such as embolism, heart failure, and sudden cardiac death. Imaging techniques, including Magnetic Resonance Imaging (MRI) and echocardiography, play a vital role in early detection, yet surgical removal remains the definitive and curative approach. Although recurrence is rare, it is more likely in individuals with hereditary conditions such as Carney complex, underscoring the importance of vigilant postoperative follow-up for these patients (18-20). Because cardiac myxomas are often clinically silent, they can lead to serious complications. The tumor's location within high-flow areas of the heart increases the risk that fragments may dislodge and embolize into systemic circulation, mimicking the behavior of aggressive malignant tumors. Consequently, undiagnosed cardiac myxomas place patients at significant risk of intracardiac obstruction and embolic events involving both pulmonary and systemic vessels, which substantially elevate morbidity and mortality, especially if the tumor is not detected promptly or incompletely resected (21-23).

Based on current knowledge, studies have indicated that certain genetic aspects can aid in the diagnosis and treatment of CM; therefore, the present study is designed to review the potential diagnostic roles of microRNAs in Cardiac Myxoma.

Genetics Aspects of Cardiac Myxoma

Approximately 10% of cardiac myxomas are associated with a hereditary condition known as Carney complex (CNC), while the majority arise sporadically without a familial link (6). Carney complex is a rare, autosomal dominant genetic disorder with variable clinical manifestations but complete penetrance, meaning that individuals who carry the mutation typically express some form of the disease (24). Although historically described as X-linked in some reports, CNC is now firmly recognized as an autosomal dominant condition (25, 26). This multisystem syndrome is defined by the presence of cardiac and extracardiac myxomas, various pigmented skin lesions, and endocrine abnormalities. Common features include cutaneous and breast myxomas, osteochondromyxomas, and myxomatous tumors of the breast, such as ductal adenomas. Skin manifestations are often notable for blue nevi and lentigines. The syndrome also involves endocrine overactivity, with manifestations such as Cushing's syndrome due to primary pigmented nodular adrenocortical disease (PPNAD), pituitary adenomas (leading to acromegaly or gigantism), thyroid nodules or carcinomas, and large cell calcifying Sertoli cell tumors (LCCST) of the testes. Additionally, psammomatous melanotic schwannomas (PMS)—a rare and pigmented type of nerve sheath tumor—are characteristic of CNC. A paradoxical increase in urinary free cortisol following low-dose

dexamethasone suppression (Liddle's test) is often observed in patients with PPNAD, further aiding in diagnosis (27-31).

The molecular basis of CNC is most commonly linked to inactivating mutations in the PRKAR1A gene, which encodes the regulatory subunit type 1-alpha (R1A) of protein kinase A (PKA). This gene is located on chromosome 17q24, and its loss of function leads to dysregulated PKA signaling, contributing to tumorigenesis in affected tissues (29, 32, 33). A definitive diagnosis of Carney complex is established when a patient exhibits two or more of the clinical manifestations associated with the syndrome, or if there is molecular confirmation of a pathogenic mutation in PRKAR1A (24). Compared to sporadic cardiac myxomas, those associated with CNC tend to present at a younger age, with a median age around 20 years, and more frequently in male patients. These tumors are often multicentric, affecting multiple cardiac chambers simultaneously or sequentially. Importantly, they carry a higher risk of recurrence, which necessitates long-term clinical surveillance even after successful surgical resection (34-36).

MicroRNAs

MicroRNAs (miRNAs) are small, non-coding RNA molecules that regulate gene expression at the post-transcriptional level by binding to complementary sequences on target messenger RNAs (mRNAs), leading to mRNA degradation or translational repression. These molecules play pivotal roles in virtually all essential cellular processes, including differentiation, proliferation, apoptosis, and metabolism. In recent years, miRNAs have garnered increasing attention as potential biomarkers and therapeutic targets due to their involvement in the pathophysiology of various diseases (37, 38). One remarkable feature of miRNAs is their ability to regulate multiple genes simultaneously, influencing diverse signaling pathways. Conversely, individual mRNAs are often regulated by a network of miRNAs, highlighting the intricate regulatory landscape controlled by these molecules (39, 40). Despite their typically modest effects on individual targets, therapeutic modulation of miRNAs, using mimics to enhance or antagonists to inhibit their activity, holds substantial promise for managing a wide array of pathological conditions (41).

The role of miRNAs in cardiac physiopathology

In recent years, a growing body of evidence has highlighted the critical role of miRNAs in both cardiac development and the maintenance of heart function, particularly under ischemic conditions (42, 43). Among these, miR-1 and miR-133a have been identified as key regulators during the early stages of heart formation. They guide the differentiation of embryonic stem cells and mesodermal precursors toward a cardiac muscle lineage, shaping the foundational architecture of the heart. These same miRNAs also influence the fate decisions of pluripotent stem cells toward mesodermal and cardiac lineages (44).

As cardiac development progresses, other miRNAs such as miR-208 and miR-499 take on essential roles by driving the maturation of cardio-blasts into fully functional cardio-myocytes and determining muscle fiber type (45, 46). While miR-1 and miR-133a are primarily involved in maintaining the heart's rhythmic activity, miR-208 and miR-499 regulate the expression of contractile proteins critical for muscle performance.

Alterations in the expression of these cardiac-specific miRNAs are frequently observed in various forms of heart disease. These changes contribute to both acute responses, such as ischemia-reperfusion injury and apoptosis, and chronic conditions, including fibrosis, hypertrophy, and structural remodeling of the heart. Notably, circulating levels of cardiac miRNAs are significantly elevated during acute myocardial infarction, positioning them as potential early biomarkers for diagnosis (47-49).

Recent studies have also expanded our understanding of miRNAs in valvular heart diseases. In the context of aortic stenosis, miR-30b appears to play a protective role by suppressing valve calcification through inhibition of osteoblastic differentiation (50). Conversely, downregulation of miR-141 has been linked to enhanced expression of Bone Morphogenetic Protein 2 (BMP-2), a key driver of osteogenic activity, ultimately

contributing to leaflet calcification and reduced valve elasticity (51).

Unlike many other areas of cardiovascular research, the role of microRNAs in cardiac tumors remains poorly understood, largely due to the scarcity of cohesive studies and the fragmented nature of the available literature.

miRNAs and Cardiac Myxoma

Cardiac myxomas, the most frequently encountered primary tumors of the heart, are typically localized in the atrial chambers and are characterized by a myxoid stroma abundant in acid mucopolysaccharides and diffusely distributed stromal cells. While histologically benign, these tumors can have severe clinical implications due to their potential to embolize or induce functional stenosis of heart valves. Advancements in gene expression profiling and immunohistochemical techniques have provided substantial evidence that myxoma cells originate from multipotent mesenchymal progenitor cells (18, 52). These tumor cells exhibit a distinct immunophenotype—c-kit-positive, but negative for cluster of differentiation (CD45) and CD31—suggesting a non-hematopoietic, non-endothelial origin. Functionally, they are capable of producing the gelatinous extracellular matrix typical of myxomas and demonstrate properties such as clonogenicity, self-renewal, and the ability to form spheroid structures, all of which are indicative of stem-like behavior (53, 54). A study by Scalise et al. further revealed that myxoma cells possess a microRNA (miRNA) expression profile that closely mirrors that of cardiac stem/progenitor cells from healthy myocardium, with notable deviations, including the upregulation of miR-126-3p and the downregulation of miR-335-5p (55). These miRNAs play pivotal roles in regulating cell proliferation, differentiation, and transformation. The subset of myxoma-initiating cells—defined by their c-kit positivity and lack of CD45 and CD31 expression—can exert pathological effects when miRNA regulation is disrupted. Specifically, the downregulation of miR-335 has been associated with the derepression of target genes like runt-related transcription factor 2 (RUNX2), which drives mesenchymal stem cell differentiation towards a reparative phenotype. This phenotype is marked by enhanced proliferative, migratory, and differentiation capacities, potentially contributing to myxoma formation (56-58). Moreover, the miRNA dysregulation, particularly the suppression of miR-335, can be induced by pro-inflammatory signals such as interferons (59). This finding provides a plausible explanation for tumor recurrence when remnants of myxoma tissue remain following surgical resection. Notably, miR-335 plays a central role in modulating the reparative functions of mesenchymal stem cells (60, 61), and its expression may serve as a valuable biomarker for assessing the therapeutic potential of stem cell-based interventions in future clinical research.

Zhang et al. reported a significant reduction in miR-217 expression within cardiac myxoma tissues. Functional analyses demonstrated that restoration of miR-217 levels in primary myxomatous cells led to suppressed cell proliferation and enhanced apoptosis. Importantly, an inverse relationship was observed between miR-217 and interleukin-6 (IL-6) expression, with further validation showing that miR-217 directly binds to the 3′-untranslated region (3′-UTR) of the IL-6 gene (62). These findings position miR-217 as a potential tumor suppressor in the context of cardiac myxoma and suggest that therapeutic modulation of this miRNA may offer a novel approach to treatment. In a similar vein, Cao et al. demonstrated that reduced expression of miR-218 facilitates increased cellular proliferation in myxomatous tissue (63). These studies support the concept that both miR-217 and miR-218 function as tumor suppressors and represent promising molecular targets for future preventive and therapeutic strategies in cardiac myxoma management.

In a recent study, Yan et al. identified distinct circulating microRNA (miRNA) expression profiles in the serum of patients diagnosed with cardiac myxoma. Specifically, four miRNAs were found to be significantly dysregulated when compared to healthy individuals: miR-320a and miR-1249-5p were notably upregulated, whereas miR-634 and miR-6870-3p were downregulated. Subsequent bioinformatic analyses revealed that miR-320a alone is predicted to regulate

nearly 500 target genes, many of which are implicated in critical biological pathways, including bone morphogenetic protein signaling, nicotinamide adenine dinucleotide metabolism, and ceramide biosynthesis (64). Functionally, the overexpression of miR-320a appears to exert anti-proliferative effects by suppressing key regulatory genes such as vascular endothelial growth factor (VEGF) and myocyte enhancer factor 2D (MEF2D), leading to reduced cellular migration and growth arrest. Conversely, miR-634, previously characterized as a tumor suppressor in various other malignancies, was found to be significantly downregulated in patients with myxoma (65, 66). This observation suggests a potentially important role for miR-634 in the pathogenesis or progression of cardiac myxomas, highlighting its relevance as a candidate biomarker or therapeutic target.

Qiu et al. explored the regulatory interplay between microRNAs, transcription factors, and the pathogenesis of cardiac myxoma. Their findings revealed an inverse relationship between the expression of peroxisome proliferator-activated receptor gamma (PPARγ) and MEF2D, the latter being a recognized biomarker of cardiac myxoma. The study demonstrated that PPARγ suppresses MEF2D expression through the upregulation of miR-122, which operates via two distinct mechanisms: by directly targeting the 3′-untranslated region (3′-UTR) of MEF2D mRNA to inhibit its expression, and by binding to a specific region in the promoter of miR-122 to enhance its transcription. Experimental data further confirmed that this miR-122-mediated repression of MEF2D inhibits the proliferation of myxoma cells, suggesting that the PPARγ/miR-122/MEF2D signaling axis plays a critical antiproliferative role in cardiac myxoma biology (67). These results point to this pathway as a potential therapeutic target. Furthermore, MEF2 transcription factors are known to stimulate the expression of miR-1, which is essential for the differentiation of embryonic stem cells into mesodermal cardiomyocytes (68). Notably, MEF2 is aberrantly upregulated in cardiac myxoma tissue, leading to excessive production of miR-1. This overexpression may contribute to the pathological differentiation of embryonic cells with neoplastic potential, thereby implicating the MEF2/miR-1 axis in the tumorigenic process of myxoma development (55). (Table 1)

Table 1. Summary of key microRNAs implicated in cardiac myxoma pathogenesis and potential clinical relevance

microRNA	Expression Pattern in CM	Primary Targets / Pathways	Functional Role	Potential Clinical Application
miR-217	↓	IL-6	Tumor suppressor (inhibits proliferation, promotes apoptosis)	Biomarker, therapeutic target
miR-218	↓	MEF2D	Tumor suppressor (inhibits proliferation)	Biomarker, therapeutic target
miR-335	↓	RUNX2	Regulates mesenchymal stem cell differentiation; recurrence risk	Prognostic marker
miR-122	↑	MEF2D (via PPARγ axis)	Anti-proliferative	Therapeutic target
miR-320a	↑	VEGF, MEF2D	Anti-proliferative, inhibits migration	Circulating biomarker
miR-634	↓	Multiple tumor pathways	Tumor suppressor	Circulating biomarker

↑ : upregulated; **↓ :** downregulated;

Abbreviation : CM : cardiac myxoma; **MEF2D :** myocyte enhancer factor 2D; **VEGF :** vascular endothelial growth factor; **RUNX2 :** runt-related transcription factor 2; **PPARγ :** peroxisome proliferator-activated receptor gamma.

This review synthesizes the most up-to-date evidence on the role of microRNAs in cardiac myxoma, integrating molecular, pathological, and clinical perspectives. By summarizing findings from both tissue-based and circulating miRNA studies, it highlights potential diagnostic biomarkers and therapeutic targets that may shape future precision medicine strategies for this rare cardiac tumor. A key strength is the comprehensive inclusion of diverse molecular pathways, such as miR-217, miR-218, miR-335, miR-122, and miR-634, along with their functional implications in tumor suppression, proliferation, and recurrence.

However, the review is limited by the scarcity and heterogeneity of available studies, many of which are based on small patient cohorts or preclinical models, restricting the generalizability of the findings. Additionally, most studies are observational and cross-sectional, making it difficult to establish causal relationships between specific miRNA alterations and disease progression. Finally, the lack of large-scale validation studies and standardized methods for miRNA detection hinders the immediate translation of these findings into clinical practice.

Conclusion

Cardiac myxomas, although histologically benign, can pose a significant clinical risk due to their potential for embolization and intracardiac obstruction. The role of microRNAs in the pathogenesis of cardiac myxomas is increasingly recognized, with specific miRNAs such as miR-217, miR-218, miR-122, and miR-335 demonstrating critical functions in tumor suppression, proliferation, and cell differentiation. Dysregulation of these molecules contributes to both tumor growth and recurrence. Additionally, distinct circulating miRNA profiles offer promising opportunities for non-invasive diagnosis and prognostic monitoring. Future research should focus on validating these biomarkers in larger cohorts and exploring therapeutic strategies that modulate miRNA expression to prevent recurrence and improve outcomes. The integration of miRNA-based diagnostics and therapeutics may revolutionize the clinical management of cardiac myxoma in the coming years.

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