Narrative Review Article

Exosomal miRNAs as Biomarkers for Tissue Degeneration

Arjun Macha

Acton Boxborough Regional High School, 36 Charter Rd, Acton, MA 01720, United States

ABSTRACT

Tissue degeneration, especially cardiac tissue degeneration, is increasingly becoming a wider cause of death. The detection of tissue degeneration is often too late, because the difficulty of detection only becomes apparent after large damage occurs. Biomarkers are used to track the progression of diseases. As levels elevate or decrease, they can tell us the constant development of a disease. The problem is that normal biomarkers, such as circulating proteins, are often unusable. They degrade too easily by enzymes, and do not provide any specificity from disease to disease. A better solution to this problem is the use of exosomal miRNA as biomarkers. Exosomal miRNA is not only resistant to degradation by enzymes but is also specific to a certain stressor. This allows us to track the levels of microRNA (miRNA) in body fluids to track the progress of a disease and discerning it from other diseases. To be able to detect changes in levels of miRNA it allows us to recognize if tissue degeneration occurs. Unlike circulating protein biomarkers that are common throughout the body, certain types of miRNAs can be regulated depending on where the degeneration occurs. For certain diseases, stress of cells starts a specific pathway that either increases or decreases the production of a specific miRNA. These pathways are regulated by proteins that bind to miRNA and guide them to secretion.

Keywords: Exosomal miRNA; tissue degeneration; miRNA sorting mechanisms; exosomal biomarkers; miRNA biomarkers

INTRODUCTION

Tissue degeneration is a defining factor of many chronic and age-related diseases, which include cardiovascular disease, neurodegeneration, kidney fibrosis, and musculoskeletal disorders (1-4). Degeneration is the progressive loss of cellular structure and function, which can lead to impaired organ performance and reduce quality of life. Detecting degeneration before irreversible damage occurs, still remains a basic challenge in modern medicine (2). Usually used biomarkers, such as circulating proteins or imaging modalities, only appear after great degeneration has taken place. As a result, the development of more sensitive, and minimally invasive biomarkers is important to advance diagnostics and the effectiveness of treatment.

A more promising and effective biomarker is exosomal miRNAs. Exosomes are small extracellular vesicles that are secreted by all cell types, and carry proteins, lipids and nucleic acids. miRNAs packaged within these exosomes reflect the state of the cell from which they were secreted and regulate gene expression and influence biological processes (2). More importantly, miRNA contained in exosomes are protected from

Corresponding author: Arjun Macha, E-mail: arjunmacha9@gmail.com.

Accepted December 8, 2025
https://doi.org/10.70251/HYJR2348.36944951

degradation by enzymes. Exosomal miRNA is highly sought after because of their specificity. Unlike many protein-based biomarkers, which are expressed across tissues, miRNAs are tissue-enriched, meaning higher expression in certain tissues, but they are not exclusive to a single cell type. For example, certain cardiac-specific miRNAs, such as miR-208 and miR-499, are released during myocardial infarction (5). Similarly, miRNAs that are found in the brain have been found to provide insight into Alzheimer's disease, specifically of synaptic dysfunction and neuronal loss (3). Exosomal miRNAs can be tracked through patient biofluids, which include blood, and cerebrospinal fluids. This easy access makes these biomarkers non-invasive. Techniques such as next-generation sequencing, and qRT-PCR, have made tracking exosomal miRNA levels easier (2). Certain tissues elevate miRNAs levels under stress, while others decrease levels, a pattern that will be explored later in the paper. With constant, or continued tracking of these levels, detection of stress and injury can be done earlier and quickly. This allows us to raise the question of how exosomal miRNAs can be used as non-invasive biomarkers of tissue degeneration (2). This review explores how exosomal miRNAs function as non-invasive biomarkers for tissue degeneration, focusing on their biological mechanisms, selective loading, diagnostic applications, and cross-tissue relevance.

EXOSOMES AND EXOSOMAL MIRNAS AS NON-INVASIVE BIOMARKERS OF TISSUE DEGENERATION

Exosomes are nanosized extracellular vesicles (30-150nm) secreted by almost all cell types and play crucial roles in intercellular communication by transporting biomolecules, including proteins, lipids, and nucleic acids. These vesicles come from the inward budding of the endosomal membrane, leading to the formation intraluminal vesicles (ILVs) inside multivesicular bodies (MVBs), which fuse with the plasma membrane to release exosomes into the extracellular space (6). Upon fusion of MVBs with the plasma membrane, IVLs are released as exosomes into the extracellular space, where they are taken up by cells through endocytosis. The lipid bilayer structure of exosomes protects their cargo from enzymatic degradation, which allows them to circulate in various bodily fluids, including blood, urine, saliva and cerebrospinal fluid (7). This stability and accessibility provide exosomes with great potential to be used as non-invasive biomarkers.

Secretion and Content of Exosomes

The creation of exosomes is controlled by endosomal sorting complexes required for transport, which are the endosomal sorting complexes required for transport (ESCRT)-dependent and -independent pathways (Figure 1). Exosomes display a distinct composition that reflects their cell of origin, inkling tetraspanins (CD8, CD82, CD63), heat shock proteins, and endosomal sorting proteins such as ALiX and TSG101 (8). This molecular specificity allows them to act as carriers of disease-specific signals and be used for diagnostic purposes. Due to their small size and membrane composition, exosomes can move through many barriers, such as the blood-brain barrier, making them particularly used in biomarker research for neurodegenerative and systemic diseases (9).

MicroRNAs (miRNAs) are short (~22 nucleotides), non-coding RNA molecules that regular gene expression after transcription, mainly through binding to complementary sequences in the 3' untranslated region

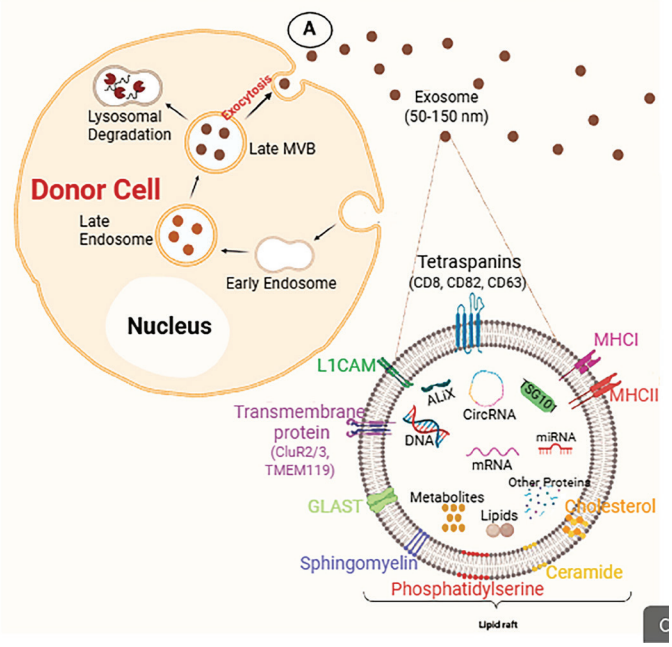

Figure 1. Mechanism of exosome biogenesis and content. Exosomes are formed by inward budding of the endosomal membrane, which generates intraluminal vesicles (ILVs) within multivesicular bodies (MVBs). These MVBs fuse with the plasma membrane and are released into the extracellular space. Exosomes carry proteins (tetraspanins CD8, CD82, CD63; ALiX; TSG101), lipids, and nucleic acids, reflecting the physiological state of the origin cell.

of target mRNAs (8). The biogenesis of miRNAs begins in the nucleus, where primary miRNA transcripts (pri-miRNAs) are transcribed by RNA polymerase II. These pri-miRNAs are split by the Drosha-DGCR8 protein complex into precursor miRNAs (pre-miRNAS), which are then exported to the cytoplasm by Exportin-5. In the cytoplasm, the enzyme Dicer further processes the pre-miRNAs into mature miRNA duplexes, one strand of it is the guide strand, is included into the RNA-induced silencing complex (RISC) to exert regulatory functions (8). By regulating the expression of multiple genes at the same time, miRNAs become key regulators in processes such as cell proliferation, apoptosis, differentiation, and stress response (10). For example, certain miRNAs are known to promote inflammation and matrix degradation degenerative joint diseases, while others may use protective effects by regulating anabolic pathways (1). In pathological conditions such as neurodegeneration, musculoskeletal diseases, cardiovascular disorders, and cancer, the dysregulation of miRNA expression has been put into use (2).

Exosomal miRNAs are an intersection and combination between exosomes and miRNAs. Encapsulation within exosomes protects miRNA from RNases that are present in circulation, which extends their half-life and preserves their functional integrity (9). Furthermore, the release of specific miRNAs within exosomes is not random, but regulated by cellular sorting mechanisms that selectively package certain miRNAs for transport, as will be discussed later on (3). This selective loading means that exosomal miRNA portrayal can reflect the physiological or pathological state of the originating cells, making them useful indicators of disease processes (2). For example, exosomal miR-21 and miR-124 have been identified as elevated in models of neuroinflammation and neuronal injury, which directly correlates to disease severity (7).

The application of these exosomal miRNAs as non-invasive biomarkers of tissue degeneration has been gaining increased popularity over the years. Normal and traditional diagnostics using biomarkers are invasive, painful, and difficult to replicate, especially during progressive diseases. However, analysis of exosomal miRNA allows for repeated monitoring through minimally invasive methods such as drawing out blood or urine collection (7). This analysis of disease progression using these miRNAs allows treatment to be effective (4). It is extremely necessary and relevant in these progressive and degenerative diseases where early detection can improve the outcome of the treatment.

There are two recent experimental studies that provide evidence for the use of exosomal miRNAs in diagnostic practices. Zhang *et al*. (2010) showed that miR-29b levels taken from plasma were significantly decreased in patients with early-stage osteoarthritis, which connects with MRI-based cartilage degeneration (8). Similarly, Cacchiarelli D (2011) found multiple exosomal miRNAs, including miR-206 and miR-133a, that were at high levels in those with early-stage Duchenne muscular dystrophy. After therapy, these levels would decrease and go to normal tracked levels (1). These findings not only show the specific uses of exosomal miRNAs disease to disease, but also highlight how they can be analyzed alongside the progression of a disease.

The potential of exosomal mRNA in diagnostics can also be found in their responsiveness to pathological changes. This means that they can be analyzed for real-time monitoring of the progression of a disease or treatment response. Especially in degenerative diseases, where early detection is beneficial, exosomal miRNAs could serve as a solution. Furthermore, their appearance in different body fluids allow for easy accessibility as in saliva for neurological disease biomarkers, and urine for kidney diagnostics (2).

Overall, the integration of exosomes with miRNA research has opened the use of exosomal miRNA as non-invasive biomarkers of tissue degeneration. There are ongoing advances in high throughput sequencing, exosome isolation techniques, and bioinformatic analysis, which are expected to further improve the specificity of exosomal miRNA. Allowing them to be quickly transitioned into clinical applications (11).

Selective Loading Mechanisms of Exosomal miRNAs

Exosomal miRNAs are becoming recognized as molecules of intercellular communication. They operate through a chain of events: biosynthesis, and selective loading, release into the extracellular environment, being picked up by the receiving cell, and finally regulating the target gene expression. Later in the paper, loading mechanisms and their importance for cell function will be discussed.

miRNAs are non-coding RNAs that regulate gene expression post-transcription by guiding the RNA-induced silencing complex (RISC) to complementary messenger RNAs (mRNAs) leading to degradation (6). They are produced starting in the nucleus, where RNA polymerase II transcribes miRNA genes into primary miRNAs (pri-miRNAs). These are processed by the microprocessor complex, which comprises Drosha and

its cofactor DGCR8, into precursor miRNAs (pre-miRNAs) (7). These pre-miRNAs are then exported into the cytoplasm by Exportin-5, where the RNase III enzyme dicer splits them into separate mature miRNA parts (8). The selective combining of miRNAs into exosomes is not a constant process, but is controlled by specific RNA-binding proteins and recognition motifs (10).

For example, sumoylated heterogeneous ribonucleoprotein A2B1 (hnRNPA2B1) recognizes GGAG motifs within miRNAs and controls their sorting into ILVs during MVB formation (6). By recognizing these specific sequences, it can guide the miRNA to exosomes as hnRNPA2B1 binds to miRNAs through its sumoylation-dependent pathways. The sumoylation-dependent pathway is a cellular process where SUMO (Small Ubiquitin-like Modifier) proteins are attached to target proteins to help regulate their function (8). Another pathway includes ceramide-dependent sorting. The neural sphingomyelinase 2 (nSMase2)-dependent pathway influences ceramide production, which enables the budding of exosomal membranes and the addition of specific miRNAs (9). Inhibiting changes in nSMase2 results in the changing of the miRNA that is selected and packaged into the exosome. The ESCRT-independent pathway also contributes to this process, as it relies mainly on lipid composition and less on protein changes. Other binding proteins, which include Y-box protein 1 (YBX1) and major vault protein (MVP, also contribute to this specific loading (3). Evidence shows that the sorting of exosomal miRNAs can also be in response to external cellular signals, or stress, which can reflect changing physiological states. One example is miR-150 which is secreted by monocytes during an inflammatory stimulus and is then taken up by endothelial cells, boosting their movement through the body (8). This shows that miRNA sorting is not only specific to diseases but dependent on the status of the environment around it.

The process of sorting is often influenced by the state of the origin cell. Under stressful conditions such as oxidative stress, mechanical injury, or inflammatory cytokine exposure, cells can alter their miRNA expression and selectively package pro-degenerative miRNAs into exosomes (2). To package pro-degenerative miRNA into the exosomes, the sorting is regulated by pathways activated through stress. These include p53, NF-κB, and MAPK cascades, which shift the cell's transcriptional and post-transcriptional process toward producing the pro-degenerative miRNA. Finally, to be transported the ESCRT and ceramide-dependent pathways help control the formation of the vesicle that the miRNA is packaged into (7).

In degenerative joint disease, chondrocytes exposed to interleukin-1β (IL-1β) secrete exosomes that contain miR-449a-5p, which are shown to promote extracellular matrix (ECM) degradation by targeting certain anti-catabolic genes (4). By tracking the changing miRNA levels, the degradation disease can be found in earlier stages, as opposed to later. Similarly, in cardiac fibroblasts, transforming growth factor-beta (TGF-β) signaling starts the packing of miR-21-5p into exosomes, which can later stimulate fibrotic pathways into the nearby cells (5). All in all, the selective loading of miRNA into exosomes is what highlights it as a useful biomarker, being able to distinguish itself between different diseases.

UPTAKE AND FUNCTIONAL ROLES IN TARGET CELLS

Once released into the extracellular space, exosomes travel through bodily fluids, such as blood, cerebrospinal fluid and synovial fluid, to reach target cells (4). They are taken up by different mechanisms that are cell type dependent, involving clathrin-mediated endocytosis, or direct fusion with the plasma membrane (12). The way an exosome enters a cell can influence what will happen to the miRNA cargo, including its release into the cytoplasm and incorporation into the target's cell's RISC mechanism (12).

Exosomal miRNAs are emerging as candidates for disease biomarkers, due to their specificity, their characteristics as a stable vesicle, and accessibility in various biological fluids. Their use as biomarkers is rooted in the fact that the miRNA can be selectively sorted, allowing them to reflect the status of their originating cell. Also, because exosomal miRNAs are protected from enzymatic degradation they are not degraded rapidly by RNases in the extracellular space (12). Exosomal miRNAs begin in the nucleus and are processed into mature miRNAs by Drosha, then connecting with RNA-binding proteins that guide them to MVBs (7). Inside MVBs different mechanisms are used, such as hnRNPA2B1 motif recognition, nSMase2-dependent ceramide signaling, or Ago2 trafficking (6). Once released depending on stress and other factors of the cell, clinicians can detect this increase or sometimes decrease in levels of miRNA. Through body fluids such as blood, the use of these miRNA biomarkers is non-invasive and specific (2).

DETECTION OF miRNAs

Tracking and measuring exosomal miRNAs for diagnostic purposes includes many standardised isolation and profiling techniques. The most widely used methods include, ultracentrifugation, ultrafiltration, precipitation-based kits, size exclusion chromatography, and immunoaffinity capture. Ultracentrifugation is the most widely used for research applications, because it is able to yield pure vesicle populations (13). Immunoaffinity capture uses antibodies against exosomal surface proteins such as CD63, CD81, and CD9, which enable isolated targeting of exosomes from specific cell origins (14). There are many traditional ways to detect miRNA, these include northern blotting, microarray analysis, and quantitative polymerase chain reaction (qPCR). Among these traditional techniques the most commonly used is northern blotting. These technologies are not only used for the detection of mature miRNAs, but also precursors of miRNA (14). Once the exosomes are isolated, the RNA that is extracted usually using pheno-chloroform-based protocols or column-based kits used for small RNAs, which allow for minimal loss of the miRNA when contained within a vesicle (14).

After the RNA is extracted, the detection and measure of exosomal miRNAs are performed through quantitative reverse transcription polymerase chain reaction (qRT-PCR), next-generation sequencing (NGS), or microarray-based approaches (2). However, NGS gives a most comprehensive depiction of the entire exosomal miRNA, which can make it easier for the discovery of new candidates for biomarkers (15). Microarrays are less sensitive to low-abundance miRNAs, but they are cost effective for large scale screening (16).

There is an essential feature that makes exosomal miRNA suited to be disease biomarkers, and it is their ability to discriminate between disease states, predict the progression of a disease, and be used to monitor treatment responses. For example, different exosomal miRNA have been identified in cancer patients compared to healthy people, with some of the miRNA being upregulated or downregulated with tumor stage or metastatic position (17). In cardiovascular diseases, specific exosomal miRNAs are high in plasma after myocardial infarction and can be detected within hours (2). Similarly, in neurodegenerative disorders such as Alzheimer's disease, exosomal miRNAs from the brain, mainly taken from the plasma or cerebrospinal fluid have been shown to correspond with amyloid-beta and tau pathology, providing a small window into diseases occurring in the central nervous system (10).

Because exosomal miRNAs can be sampled many times through non-invasive or minimally invasive procedures, they can serve as biomarkers to monitor therapeutic effects, or detection of disease. There have been many analytical advancements that have increased the capability of quantifying exosomal miRNAs from small sample volumes. Emerging microfluidic systems can integrate exosome isolation, RNA extraction, and miRNA detection, which significantly reduces assay time and enables use in clinical settings (7). However, despite these advantages the movement of exosomal miRNA biomarkers into a clinical routine poses many challenges. Pre-analytical variability, including differences in the collection of biofluid, storage, and processing of the miRNA, can influence exosomal miRNA profiles and be unusable across studies (1). Furthermore, without having a common technique for exosomal miRNA quantification, it complicates data interpretation especially when working with others (8).

EXOSOMAL miRNAs AS BIOMARKERS OF CARDIAC TISSUE DEGENERATION

Exosomal miRNAs emerge as tools for monitoring tissue degeneration because of their stability, and specificity. Unlike free-circulating RNAs which are degraded in blood, miRNAs encapsulated within exosomes remain stable, and less likely to be degraded (6)(7). This stability makes them useful as non-invasive diagnostic testing through blood, and other body fluids (2). Most importantly, the miRNA chosen to be encapsulated in exosomes is not random but is selectively chosen to reflect the state of the cell itself. This means that the miRNA profile of exosomes can mirror the changes occurring within degenerating tissue cells (8).

Compared to traditional protein biomarkers, exosomal miRNAs are better because of their higher tissue specificity. For example, cardiac troponins are used widely to diagnose myocardial injury, but they mainly reflect necrosis and do not show the more subtle changes such as fibrosis, metabolic remodeling, or apoptosis (7). Exosomal miRNAs are different, they provide information while the disease is occurring (7). They can increase or decrease depending on the activation of stress factors, inflammatory signaling cascades, or apoptotic regulators in affected tissue (9)(10). Which shows how easily they can be tracked and shows the progression of a disease.

The use of exosomal miRNA as biomarkers is increased by the availability of detection methods, such

as those mentioned previously. These techniques allow for profiling of miRNAs that are taken at very low concentrations, which opens their use to early-stage detection (1). The use of exosomal miRNAs as biomarkers has increased in popularity with cardiovascular diseases leading in usage. The heart provides a great example of how exosomal miRNAs can serve as indicators of tissue degeneration. Cardiovascular degeneration contains many processes, such as myocardial infarction (MI), ischemic injury, and cardiac fibrosis. Each of which has distinct changes in the miRNA, which can reflect the situation the cells are in (1)(2).

One studied case is the release of exosomal miR-133a and miR-1 which are released during acute myocardial infarction. In myocardial infarction the myocardium is blocked, and without oxygen and nutrients, the tissue downstream suffers (4). The cells do not get oxygen, and therefore undergo necrosis, which is uncontrolled cell death, and apoptosis. The lack of oxygen causes stress in the heart muscle cells. This stress then activates signaling pathways, like hypoxia-inducible factor (HIF) and reactive oxygen signaling (4). Under stress, the cell changes its exosomal cargo into the selected miR-133a and miR-1. This is controlled by recognition by RNA-binding proteins (RBPs) like HnRNPA2B1, and then Ago2 mechanisms to load them into MVBs (4). Elevated levels of these miRNAs can therefore serve as a real-time indicator of acute cardiomyocyte injury (4).

Another important regulator is miR-208, which is a cardiac-specific miRNA that is encoded with the α-myosin heavy chain gene (4). Exosomal miR-208 levels rise during myocardial injury and hypertrophic remodeling (4). This elevated level reflects shifts in contractile protein expression and can correlate with the development of left ventricular hypertrophy in heart failure patients (5). During this, cells switch to anaerobic metabolism, which leads to lactic acid buildup and ATP depletion. These conditions trigger birth necrosis and apoptotic signaling. Cardiac muscles have a unique group of cardiac-specific miRNAs, which are called myomiRs. Most important of which is miR-208, which is encoded in the introns of the α- and β-myosin heavy chain (MHC) genes (MYH6 and MYH7). During stress the β-MHC gene is upregulated as the myocardium tries to deal with the stress. And, because miR-208 is encoded within MYH7, levels rise (18).

Fibrosis is another mark of cardiac degeneration; in fibrosis, miR-21 plays an important role. In fibroblasts, miR-21 increases the activation of extracellular signal-regulated kinase (ERK)-MAPK signaling (19). Under degenerative conditions, fibroblasts secrete exosomes with a lot of miR-21. These exosomes can be detected in circulation and correlated with the degree of fibrosis (11). Specifically, increased exosomal miR-21 is not just a byproduct but can drive fibrotic degeneration. When taken up by cardiomyocytes, it can promote apoptosis and further tissue decline. Stress signals activate transcription factors AP-1 and NF-κB, which upregulate miR-21 expression in fibroblasts (19). Instead of staying inside the cell, a large portion of miR-21 is selected and packaged into exosomes (19). Once inside target cells, miR-21 downregulates PTEN and SPRY1, which are two negative regulators of survival and growth pathways (19). This ultimately leads to the overactivation of pro-apoptotic and pro-fibrotic signaling. By spreading these between cells it contributes to ventricular stiffening, reduced contractility, and progressive heart failure. Its importance lies in both its role inside and its utility as a biomarker for heart failure progression tracking (19).

Other exosomal miRNAs can function as negative regulators of fibrosis and degeneration, and their decline can be used as biomarkers. For example, when miR-29 is downregulated, it is consistently observed in fibrotic cardiac tissue, whether caused by ischemia, pressure overload, or diabetic cardiomyopathy (12). Detecting a reduction in circulating exosomal miR-29 can therefore signal ongoing fibrotic remodeling and can be useful in identifying patients who are at high risk of stiffened ventricles and diastolic dysfunction. In addition to apoptosis and fibrosis, metabolic changes are a component of cardiac degeneration (7). Under stress, cardiomyocytes shift from fatty acid oxidation to glycolysis; with this, there are changes to the regulatory miRNAs such as miR-499 and miR-30d (7). Exosomes containing these miRNAs can reflect the altered metabolic states (13). Detecting these changes offers identification of early metabolic changes that can be targeted before irreversible damage occurs.

Current clinical studies have been studying these connections. For instance, circulating exosomal miR-1, miR-133a, and miR-208a have been measured in acute coronary syndrome patients, where they are correlated strongly with the infarct size and left ventricular ejection fraction (14). Exosomal miR-21 and miR-29 have been related to measures of fibrosis in heart failure groups (19). While most of these studies are observational, they show that exosomal miRNAs can separate patients by severity and provide information beyond standard markers.

The techniques used to detect cardiac exosomal miRNAs rely mainly on liquid biopsy sampling (2).

Plasma or serum is collected, and exosomes are isolated through ultracentrifugation, precipitation kits or immunoaffinity capture (11). The RNA is extracted and measured using qRT-PCR or sequencing (11). Challenges still remain in standardizing isolation methods and controlling variables, but progress in microfluid-based isolation is making it easier to implement exosomal miRNA analysis and practice (2).

Altogether, the cardiovascular field shows how exosomal miRNAs can be used as clear signals of the changes occurring in the heart. They reflect processes such as cell death, scar formation, and shifts in energy use that other biomarkers miss, which makes them especially useful for monitoring disease progression and how the patients respond to treatment.

APPLICATIONS BEYOND THE HEART

Although the cardiovascular system shows the clearest demonstration of the use of exosomal miRNAs as degeneration markers, similar principles can apply across other tissues (7). In osteoarthritis, cartilage breakdown is strongly associated with altered exosomal miRNA profiles in synovial fluid (5). For example, miR-140 is normally highly expressed in healthy cartilage, where it maintains extracellular matrix homeostasis by targeting ADAMTS5, which is a major aggrecanase (5). In osteoarthritic joints, the levels of exosomal miR-140 decline, and this signals enhanced catabolic activity and matrix degradation (5). Alternatively, miR-146a, which is upregulated by NF-κB signaling in response to inflammatory cytokines, rises in osteoarthritis, also reflecting the ongoing degeneration (10).

Both of these miRNAs can be tracked and allow for early detection of osteoarthritis before irreversible damage occurs (5). In skeletal muscle degeneration such as sarcopenia or muscular dystrophy, exosomal miR-1 and miR-206 are consistently at high levels (1). These miRNAs assist muscle regeneration under normal conditions, yet their release into exosomes during degeneration reflects the apoptosis occurring. Therefore, these elevated levels serve as indicators of muscle apoptosis (1).

Neurodegeneration also exhibits changes in exosomal miRNA. In Alzheimer's disease (AD) one of the central problems is the buildup of amyloid-β (Aβ) plaques in the brain (7). These plaques form when the protein amyloid precursor protein (APP) is cut by a specific enzyme called BACE1 (β-secretase 1) (7). Normally, miR-29 levels keep BACE1 levels in check. Under healthy conditions, exosomal miR-29 binds to the mRNA for BACE1, which prevents its production. In AD, exosomal miR-29 levels decrease, which is consistent with its role in repressing BACE1, the enzyme that generates amyloid-β (7). Similarly, increased levels of miR-34a reflect apoptosis and mitochondrial dysfunction, which are both key features of AD and Parkinson's diseases (2). Because cerebrospinal fluid and plasma contain exosomes from the brain, these changes in miRNA levels can be monitored non-invasively.

The kidney is also another organ where fibrosis degeneration can be tracked through levels of miRNAs. Exosomal miR-21 levels are elevated during renal fibrosis, which shows the activation of TGF-β/Smad signaling in tubular epithelial cells (7). Conversely, reduced levels of miR-29 are an indication of loss of antifibrotic repression. These changes in miRNA levels are consistent with the patterns that are observed in cardiac fibrosis, which further highlights how exosomal miRNA can provide cross-tissue information for degenerative changes (4). Altogether, these examples display the range of applicability of exosomal miRNAs as biomarkers of degeneration. While specific miRNAs differ by tissue, there are common patterns and themes that emerge. Stress and apoptosis-associated miRNAs usually rise in level, while antifibrotic and homeostatic miRNAs usually decline. This allows exosomal miRNAs to put themselves as candidates for non-invasive monitoring of degenerative diseases across the body.

CONCLUSION

Research of exosomal miRNAs as biomarkers of tissue degeneration is an advancing field with a wide variety of implications. By packaging miRNAs into exosomes, cells can provide a real-time depiction of their status. In degenerative diseases, where early detection and constant monitoring are lacking, specifically in myocardial infarction and fibrosis, the ability to use these exosomal miRNAs becomes prominent (4). Exosomal miRNAs not only offer specificity by tissue, but also accessibility, as they can be taken from biofluids and repeated without invasive measures. By tracking miRNAs such as miR-208 and miR-499, we can see the indication of myocardial infarction, which can correlate directly with tissue injury (5). Furthermore, shifts in fibroblast and miRNAs in certain tissues can be tracked, as levels increase or decrease from normal levels. By being able to track them, it provides insight into the level of stress cells are experiencing. This example of myocardial infarction can be applied to other

places such as the kidney, musculoskeletal degeneration, and osteoarthritis (1)(5). Since the destruction of degenerative diseases is so immense, the possibility of earlier treatment and the hope of stopping it becomes important. Cardiovascular disease remains one of the leading causes of death globally, and neurodegeneration affects many with other problems (2). Tools such as exosomal miRNA, which enable earlier, more accurate detection and monitoring of these diseases, can change the pathway of treatment itself.

CONFLICT OF INTEREST

The author declares that there are no conflicts of interest regarding the publication of this article.

REFERENCES

1. Cacchiarelli D, Legnini I, Martone J, Cazzella V, *et al*. miRNAs as serum biomarkers for Duchenne muscular dystrophy. *EMBO Mol Med.* 2011 May; 3 (5): 258-65. https://doi.org/10.1002/emmm.201100133
2. Xu D, Di K, Fan B, Wu J, *et al*. MicroRNAs in extracellular vesicles: Sorting mechanisms, diagnostic value, isolation, and detection technology. *Front Bioeng Biotechnol*. 2022 Oct 17; 10: 948959. https://doi.org/10.3389/fbioe.2022.948959
3. Rajool Dezfuly A, Safaee A, Salehi H. Therapeutic effects of mesenchymal stem cells-derived extracellular vesicles' miRNAs on retinal regeneration: a review. *Stem Cell Res Ther*. 2021 Oct 7; 12 (1): 530. https://doi.org/10.1186/s13287-021-02588-z
4. Wang GK, Zhu JQ, Zhang JT, Li Q, *et al*. Circulating microRNA: a novel potential biomarker for early diagnosis of acute myocardial infarction in humans. *Eur Heart J*. 2010; 31 (6): 659-666. doi:10.1093/eurheartj/ehq013.
5. Iulian Stanciugelu S, Homorogan C, Selaru C, Patrascu JM, *et al*. Osteoarthritis and microRNAs: Do They Provide Novel Insights into the Pathophysiology of This Degenerative Disorder? *Life*. 2022 Nov 17; 12 (11): 1914. https://doi.org/10.3390/life12111914
6. Villarroya-Beltri C, Gutiérrez-Vázquez C, Sánchez-Cabo F, Pérez-Hernández D, *et al*. Sumoylated hnRNPA2B1 controls the sorting of miRNAs into exosomes through binding to specific motifs. *Nat Commun*. 2013; 4: 2980. https://doi.org/10.1038/ncomms3980
7. Mori MA, Ludwig RG, Garcia-Martin R, Brandão BB, Kahn CR. Extracellular miRNAs: From Biomarkers to Mediators of Physiology and Disease. *Cell Metab*. 2019 Oct 1; 30 (4): 656-73. https://doi.org/10.1016/j.cmet.2019.07.011
8. Zhang Y, Liu D, Chen X, Li J, *et al*. Secreted Monocytic miR-150 Enhances Targeted Endothelial Cell Migration. *Mol Cell*. 2010 July 9; 39 (1): 133-44. https://doi.org/10.1016/j.molcel.2010.06.010
9. Théry C, Ostrowski M, Segura E. Membrane vesicles as conveyors of immune responses. *Nat Rev Immunol*. 2009 Aug; 9 (8): 581-93. https://doi.org/10.1038/nri2567
10. Ye J, Xu M, Tian X, Cai S, Zeng S. Research advances in the detection of miRNA. *J Pharm Anal*. 2019 Aug 1; 9 (4): 217-26. https://doi.org/10.1016/j.jpha.2019.05.004
11. de Freitas RCC, Hirata RDC, Hirata MH, Aikawa E. Circulating Extracellular Vesicles As Biomarkers and Drug Delivery Vehicles in Cardiovascular Diseases. *Biomolecules*. 2021 Mar; 11 (3): 388. https://doi.org/10.3390/biom11030388
12. Théry C, Witwer KW, Aikawa E, Alcaraz MJ, *et al*. Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines. *J Extracell Vesicles*. 2018 Dec 1; 7 (1): 1535750.
13. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. *Science*. 2020; 367 (6478): eaau6977. https://doi.org/10.1126/science.aau6977
14. Marín RM, Vaníček J. Efficient use of accessibility in microRNA target prediction. *Nucleic Acids Res*. 2011 Jan 1; 39 (1): 19-29. https://doi.org/10.1093/nar/gkq768
15. Skog J, Würdinger T, van Rijn S, Meijer DH, *et al*. Glioblastoma microvesicles transport RNA and proteins that promote tumour growth and provide diagnostic biomarkers. *Nat Cell Biol*. 2008; 10 (12): 1470-6. https://doi.org/10.1038/ncb1800
16. Mittelbrunn M, Gutierrez-Vazquez C, Villarroya-Beltri C, Gonzalez S, *et al*. Unidirectional transfer of microRNA-loaded exosomes from T cells to antigen-presenting cells. *Nat Commun*. 2011; 2: 282. https://doi.org/10.1038/ncomms1285
17. Pegtel DM, Cosmopoulos K, Thorley-Lawson DA, van Eijndhoven MAJ, *et al*. Functional delivery of viral miRNAs via exosomes. *Proc Natl Acad Sci U S A*. 2010; 107 (14): 6328-33. https://doi.org/10.1073/pnas.0914843107
18. Cheng M, Yang J, Zhao X, Zhang E, *et al*. Circulating myocardial microRNAs from infarcted hearts are carried in exosomes and mobilise bone marrow progenitor cells. *Nat Commun*. 2019 Feb 27; 10: 959. https://doi.org/10.1038/s41467-019-08895-7
19. Surina RA, Fontanella RA, Scisciola L, Marfella R, Paolisso G, Barbieri M. miR-21 in human cardiomyopathies. *Front Cardiovasc Med*. 2021; 8: 767064. https://doi.org/10.3389/fcvm.2021.767064