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The role of microRNAs in the development of heart failure

El rol de los microRNAs en el desarrollo de la insuficiencia cardiaca

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Keywords:
MicroRNA, Heart failure, cardiac hypertrophy.

Palabras clave:
MicroRNA, insuficiencia cardiaca, hipertrofia cardiaca.

ABSTRACT

MicroRNAs are single-stranded RNA of 22 nucleotides of length. Since their description in 1993, microRNAs have gained importance due to their ability to modify the expression of other genes at a post-transcriptional level. MicroRNAs are involved in regulating cardiac hypertrophy by acting as stimulators or inhibitors of some pathways related to the cell cycle. In this review, the most relevant ones will be discussed. MicroRNA-1 is a muscle tissue-specific microRNA, is considered an anti-hypertrophic microRNA. MicroRNA-133a, expressed in cardiac muscle, is characterized by its anti-hypertrophic effect. This microRNA modifies some pathways such as calcium, cell growth and development. MicroR-185 plays an anti-hypertrophic role and has three major targets during the process: sodium/calcium transporter, nuclear factor activating T cells, and Ca2+/Calmodulin-dependent protein kinase II. MicroRNA-378, expressed in cardiac myocytes, acts as a repressor of cardiac hypertrophy. On the other hand, microRNA-155 promotes cardiac hypertrophy through calcium signaling pathways and inflammation pathways. MicroRNA-200c is considered pro-hypertrophic and is thought to inhibit the action of myosin light chain kinase. It is even possible that the concentration microRNAs give us more information about the prognosis or diagnosis of cardiac diseases in the future.

RESUMEN

Los microRNAs son RNA monocatenarios de 22 nucleótidos de longitud. Desde su descripción en 1993, los microRNAs han ganado importancia debido a su capacidad para modificar la expresión de otros genes a nivel postranscripcional. Los microRNAs están involucrados en la regulación de la hipertrofia cardíaca al actuar como estimuladores o inhibidores de algunas vías relacionadas con el ciclo celular, en esta revisión se discutirán los más relevantes. El microRNA-1, un microRNAs específico de tejido muscular se considera un microRNA antihipertrófico. El microRNA-133a, expresado en el músculo cardiaco se caracteriza por su efecto antihipertrófico, este microRNA modifica algunas vías relacionadas con el calcio, el crecimiento y desarrollo celular. MicroR-185 desempeña una función antihipertrófica y tiene tres objetivos principales durante el proceso: el transportador de sodio/calcio, las células T que activan el factor nuclear y la proteína cinasa II dependiente de Ca2+/Calmodulina. El microRNA-378, expresado en miocitos cardiacos, actúa como represor de la hipertrofia cardíaca. Por otro lado, el microRNA-155 promueve la hipertrofia cardiaca a través de vías de señalización de calcio y vías de inflamación. El microRNA-200c se considera prohipertrófico y se cree que puede inhibir la acción de la cinasa de cadena ligera de miosina. Es posible que la concentración de los microRNAs nos dé más información sobre el pronóstico o diagnóstico de enfermedades cardíacas en el futuro.

INTRODUCTION

MicroRNAs are defined as single-stranded RNA with approximately 22 nucleotides in length. Since its description in 1993, the microRNAs have gained importance due to their ability to modify the expression of other genes at a post-transcriptional level.[1,2] The microRNAs can be found attached to other intracellular or extracellular structures that prevent them from being degraded by RNases. Although between 95-99% of circulating microRNAs are attached to protein complexes, others may be encapsulated in microvesicles, apoptotic bodies, and High-density lipoprotein cholesterol (HDL-C).[3] MicroRNAs are involved

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in regulating cardiac hypertrophy by acting as stimulators or inhibitors of some pathways related to the cell cycle *(Figure 1)*.[4] In addition, it has been described that microRNAs levels may be altered in other pathophysiological mechanisms in the heart, such as remodeling, apoptosis or hypoxia, which is why they have been suggested as diagnostic or prognostic markers for heart failure.[4] The importance of the study of microRNAs is based on the discovery of new therapeutic targets that may be able to help in the treatment of heart diseases (among others) from a molecular level; initially, the knowledge of microRNAs help to understand the principles of regulation of the genetic material involved in heart diseases, especially in heart failure and how its modification or intervention could possibly replace the currently used drugs representing greater effectiveness; although this is a scenario that will occur in the future, molecular medicine has begun to move towards this type of treatment. In addition, at present, the detection of the presence of microRNAs as disease markers can help detect the development of heart failure or the risk of developing many years before any symptoms appear, this will help patients with higher risk may have a closer follow-up. Understanding the way in which microRNAs interact, in turn allows a greater understanding of pathologies. Currently, dozens of alterations in microRNA have been described in patients with heart failure; in this review, the most relevant ones will be discussed.

MicroRNA-1

MicroRNA-1 is a muscle tissue-specific microRNA abundantly expressed in the heart, and together with other microRNAs, has a significant role in the development of embryonic stem cells and cardiomyocyte progenitor cells.[5] MicroRNA-1 is considered an anti-hypertrophic microRNA because an increase in its expression is associated with less cardiac hypertrophy.[4] Some studies have shown that microRNA-1 is even important for cardiogenesis. In 2007 were described alterations in cardiogenesis in mice whose concentration of microRNA-1 had been altered *(Figure 2)*.[6]

MicroRNA-1 has an important role in regulating cardiac hypertrophy by inhibiting some pro-hypertrophic pathways such as the calcium signaling pathway. The calcium signaling pathway is a pro-hypertrophy pathway that increases intracellular calcium; by increasing intracellular calcium in the cardiomyocyte, the

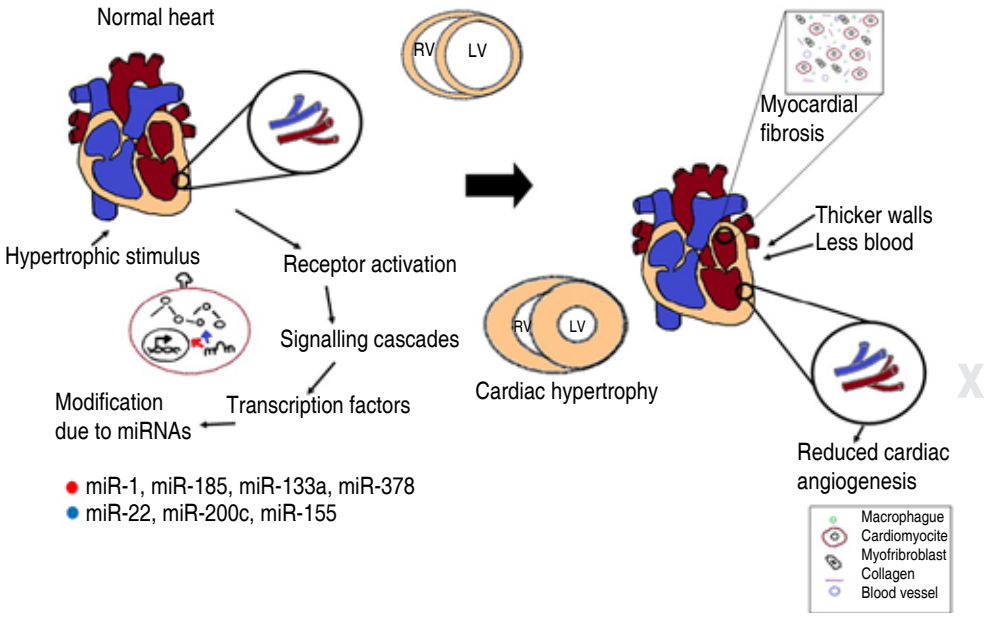

Figure 1:

A hypertrophic stimulus activates its corresponding receptor leading to a complex signaling cascade activating hypertrophic genes, like some physiological changes.
RV = right ventricle,
LV = left ventricle.

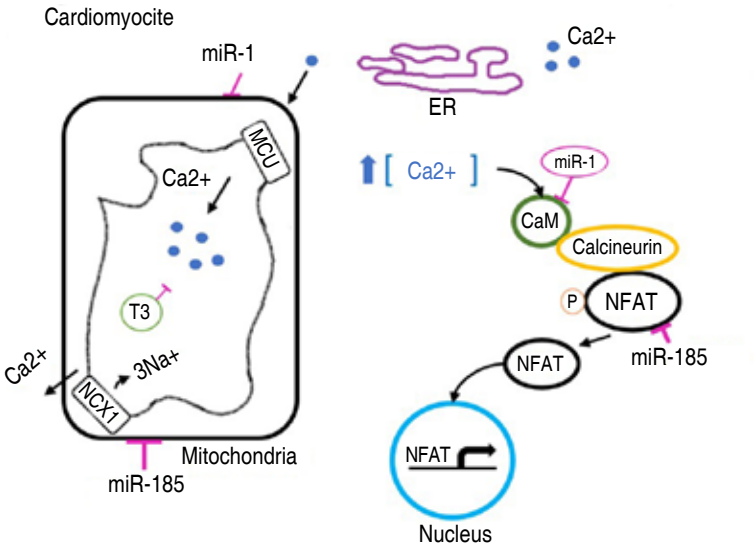

Figure 2: MicroRNA-1 downregulates the expression of crassulacean acid metabolism and directly regulates mitochondrial calcium uniporter expression during development; T3 enhances the expression level of microRNA-1, suppressor of mitochondrial calcium uniporter. MicroRNA-185 targets the sodium-calcium exchanger and nuclear factor of activated T cells 3.
MCU = mitochondrial calcium uniporter, CaM = calmodulin.

calcineurin-NFAT (Nuclear Factor of Activated T cells) pathway is activated, which causes dephosphorylation of NFAT, which leads to its translocation in the nucleus. Once inside the nucleus, the expression of NFAT increases the transcription of pro-hypertrophic genes (genes involved in the hypertrophic response). The action of microRNA-1 in the cardiomyocyte inhibits the calcineurin-NFAT pathway, which will result in the inhibition of the transcription of pro-hypertrophic genes.[7,8]

On the other hand, some authors have pointed out that this is not the only way by which microRNA-1 could regulate the entry of calcium into the cardiomyocyte. MicroRNA-1 may inhibit the mitochondrial calcium uniport, a subunit of the mitochondrial calcium uniport pore complex. This complex is responsible for introducing calcium from the intracellular space into the cardiomyocyte.[9] Some studies have indicated that in biopsies of patients with cardiac hypertrophy, microRNA-1 is decreased while this complex is increased, suggesting that microRNA-1 can regulate the expression of this complex and, therefore, inhibit cardiac hypertrophy.[10]

Another way microRNA-1 could be involved with cardiac hypertrophy is by its relationship with the thyroid hormone T-3. A study conducted in 2017 demonstrated that overexpression of microRNA-1 reduces the expression of histone deacetylase-4 (HDAC4), which attenuates thyroid hormone-induced cardiac hypertrophy.[11]

Insulin-like growth factor-1 (IGF-1) is a hormone that has been reported to induce cardiac hypertrophy and could be another target of microRNA-1. A 2009 study demonstrated that microRNA-1 is negatively correlated with IGF-1 because both IGF-1 and its receptor are targets of microRNA-1. Furthermore, it was shown that the transduction cascade regulates the expression of microRNA-1 and that microRNA-1 is inversely related to cardiac mass and myocardial thickness, suggesting that the interaction between IGF-1 and microRNA-1 has important repercussions on the myocardium.[12]

Although several studies correlate microRNA-1 with cardiac hypertrophy, there are still no sufficiently valid clinical studies to determine the usefulness of microRNA-1 in the context of heart failure. The relationship of microRNA-1 with heart failure is still under investigation. However, it is also important to mention that clinical studies suggest that microRNA-1 could be used as a marker for heart failure in the future. In 2011, a study showed that microRNA-1, along with other microRNAs, was elevated in patients with the acute coronary syndrome, proposing that microRNA-1 could be used to diagnose acute heart failure due to acute coronary syndrome[13] *(Table 1)*.

MicroRNA-133a

MicroRNA-133a is a microRNA that, like microRNA-1, is expressed in cardiac muscle and is characterized by its anti-hypertrophic effect, while microRNA-133b is specifically expressed in skeletal muscle microRNA-133a modifies some pathways such as calcium, cell growth and development.[14] Both microRNA-1 and microRNA-133a *in vitro* are deregulated during cardiac differentiation of cardiac progenitor cells (PCs), but only the expression of microRNA-133a increases under oxidative stress.[15] A study presented in 2010 quantified the serum

concentrations of various microRNAs in patients with ST-segment elevation myocardial infarction against a control group. The results showed that on day 0, microRNA-133a, microRNA-133b, microRNA-1 and microRNA-499-5p had a significant increase in serum concentration compared to the control groups.[16] On the other hand, a study in 2007 intentionally looked for a relationship between microRNA-133 and heart failure; they found a decrease in the expression of both microRNA-133 and microRNA-1 in mice and humans with cardiac hypertrophy, *in vitro* they found that the expression of microRNA-133a and microRNA-1 inhibited the development of cardiac hypertrophy. Also, *in vivo*, the infusion of antagomir (an agent that causes inhibition of microRNA-133) increased the possibility of cardiac hypertrophy *(Figure 3)*.[17]

Table 1: Differences among the microRNAs described.

microRNA	Type	Targets	Up-/down-regulated
microRNA-1	Cardiac	IGF-1R/IGF1/MCU	Downregulated
microRNA-133a	Cardiac	Gq/PKCd	Downregulated
microRNA-22	Cardiac	Sirt1/Hdac4	Upregulated
microRNA-155	Circulating	Jarid 2/AT1R/SOCS1	Upregulated
microRNA-200c	Epitelial	MLCK	Upregulated
microRNA-185	Circulating	Nfatc3/Ncx1/Camk2d	Downregulated
microRNA-378	Cardiac	Grb2/IGF1R/Mapk1	Downregulated

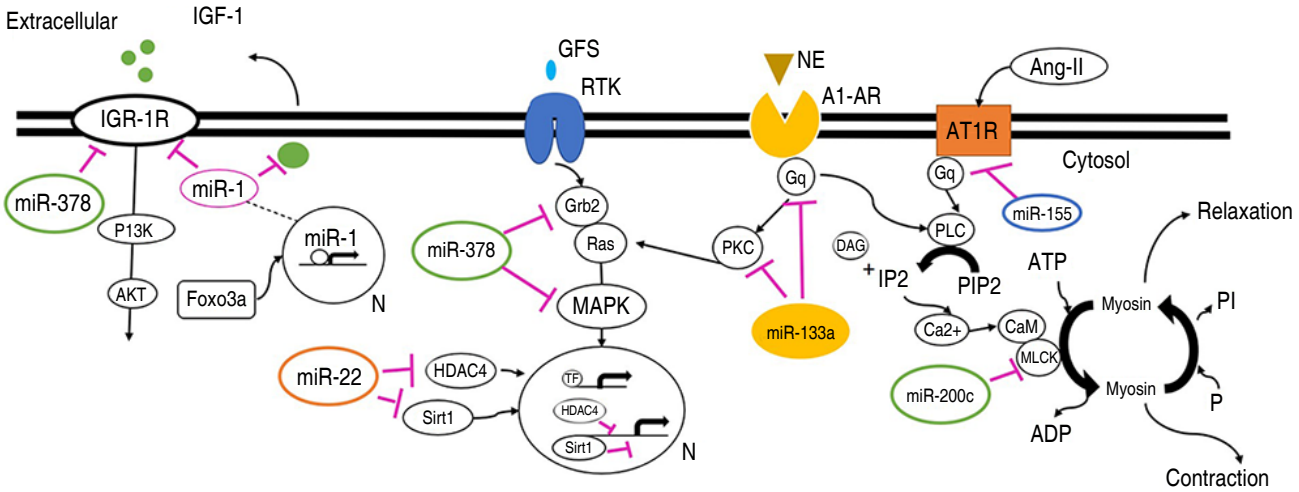

Figure 3: MicroRNA-133a attenuates cardiomyocyte hypertrophy by inhibiting protein kinase C and Gq. Alfa 1-adrenoceptor couples to G protein due to its activation by NE, resulting in the activation of phospholipase C, which activates calcium signaling pathways and the PKC-MAPK pathway (protein kinase C-mitogen-activated protein kinase pathway), increasing the expression of hypertrophic transcription factors. MicroRNA-155 attenuates Angiotensin II-induced hypertrophy through downregulating Angiotensin II type 1 receptor and its downstream Ca2+ signaling. MicroRNA-200c promotes cardiac hypertrophy by directly targeting myosin light chain kinase. MicroRNA-378 targets GRB2, thus repressing the activity of GRB2-RAS signaling. It represses mitogen-activated protein kinase, signaling by targeting mitogen-activated protein kinase 1. Both MicroRNA-378 and microRNA-1 repress insulin-like growth factor 1 receptor, but microRNA-1 also targets IGF-1 protein. The activation state of the IGF-1 signal reciprocally regulates microRNA-1 expression through the forkhead box (FOXO3a) transcription factor. MicroRNA-22 targets two histone deacetylases, sirtuin-1 and histone deacetylase 4, implying that microRNA-22 plays a role in epigenetic regulation of gene expression during cardiac hypertrophy.

The action of microRNA-133 is mainly due to the inhibition of the Gq protein and protein kinase C pathways. By binding norepinephrine to the α1 adrenergic receptors, the receptors are coupled to the G proteins, which results in the activation of phospholipase C when phospholipase C is activated, the degradation of phosphatidylinositol 4,5 bisphosphate into inositol 1,4,5 triphosphate and diacylglycerol is catalyzed, which activates calcium signaling pathways and protein kinase C pathways, resulting in transcription of hypertrophic transcription factors. By blocking the Gq protein and protein kinase C pathways, the entire cascade secondary to these is inhibited, which is why microRNA-133 has an anti-hypertrophic effect.[18]

In-vitro, the exposure of cardiomyocytes to high glucose levels produces hypertrophic changes and reduces the expression of microRNA-133a. Likewise, the levels of microRNA-133 decreased in mice after two months of having induced diabetes.[19]

MicroRNA-133 may seem like a good candidate for diagnosis or prognosis in terms of heart failure. However, until today there is no clinical study with sufficient evidence to determine the clinical use of this particular microRNA *(Table 1)*.

MicroRNA-155

MicroRNA-155, contrary to microRNA-1 and microRNA-133, is a microRNA that promotes cardiac hypertrophy through calcium signaling pathways and inflammation pathways. MicroRNA-155 may be expressed in some macrophages.[20] These macrophages expressing microRNA-155 are thought to promote cardiac hypertrophy through two pathways: the Janus kinase signal transducer (JAK) pathway and the activator of transcription 3 (STAT3) pathway; also can inhibit suppressor macrophages of cytokine-1 signaling (SOCS1), which stimulates phosphorylation of STAT3, as STAT3 is phosphorylated in macrophages, pro-hypertrophic signaling of the paracrine type is carried out in cardiomyocytes.[4]

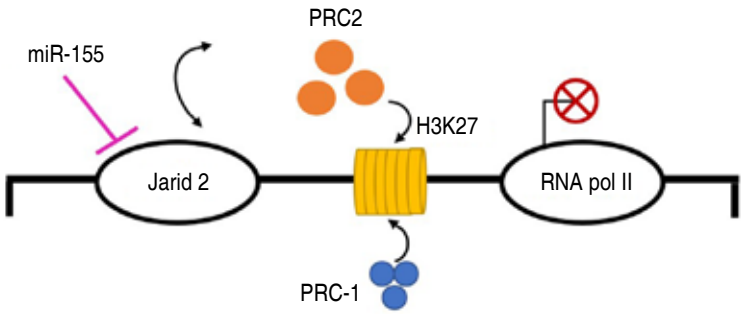

Figure 4: MicroRNA-155 inhibits Jumonji and AT-Rich interaction domain containing 2, which recruits polycomb repressive complex 2 and with polycomb repressive complex 1 repress transcription by catalyzing the histone H3K27, inhibiting RNA polymerase II.

However, this is not the only way in which microRNA-155 could induce cardiac hypertrophy. A study in 2014 suggested that microRNA-155 can induce cardiac hypertrophy by inhibiting the expression of Jarid2, a transcriptional regulator of cardiac development, since it is linked to cell proliferation.[4]

Another proposed mechanism by which microRNA-155 can induce cardiac hypertrophy is through angiotensin II. A study suggested this in 2016 after noting an increase in angiotensin I receptor levels, intracellular calcium and calcineurin beta in cardiomyocytes with microRNA-155 inhibitors and subsequently treated with angiotensin II. Since some of the microRNA-155 inhibitors do not decrease hypertrophy, it has been suggested that the inhibition of microRNA-155 and the activation of calcium pathway signaling may induce myocardial cell apoptosis, which could reduce the levels of markers of cardiac hypertrophy.[21] It has been observed that the CYTOR gene (Cytoskeleton Regulator RNA), a non-coding RNA chain that is over-expressed in cancer cells, is up-regulated in cardiac and hypertrophic cardiomyocytes; they also deduced that knock-down of this gene increases angiotensin II levels in the cardiac hypertrophy *(Figures 4 and 5) (Table 1)*.[22]

Other microRNAs

In 2009 evaluated the myocardial expression of various microRNAs in patients with heart failure before and after treatment with ventricular assist devices. Their study reported that 71.4 % of microRNAs were regular after treatment, suggesting that microRNAs could be used as a

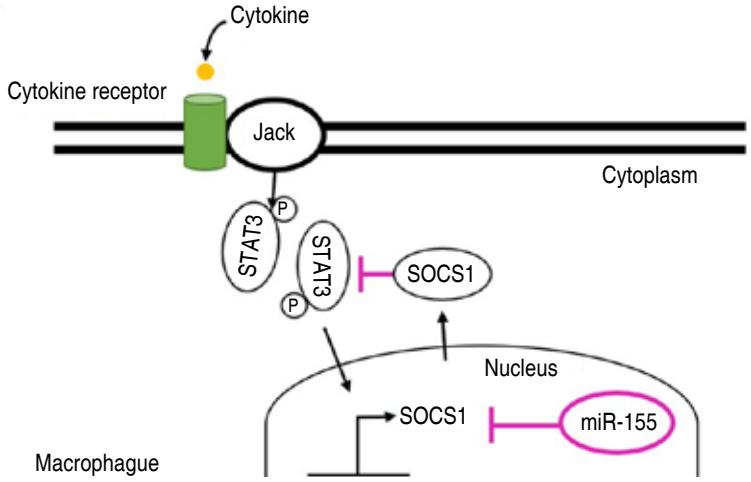

Figure 5: MicroRNA-155 silences suppressor of cytokine signaling 1, a negative regulator of the Janus kinase/signal transductor and activator of transcription signaling pathway.

marker of recovery after treatment.[23] Like this study, many authors have described alterations in plasma concentrations or tissue expressions in many diseases. However, in many cases, little is known about how microRNAs interact in the course of some diseases. In this section, we will discuss some microRNAs in which has been described that they play a secondary role in heart failure.

MicroRNA-22 is a microRNA expressed mainly in cardiac muscle and skeletal muscle and is stimulated during cardiac hypertrophy and myocyte differentiation. This microRNA is essential for cardiac development and morphogenesis.[24] MiR-22 is considered a pro-hypertrophic microRNA; some authors have suggested that microRNA-22 could inhibit sirtuin 1 (SIRT1) and histone deacetylase 4 (HDAC4), which are considered protective for cardiac hypertrophy.[4,25] It has also been observed that the overexpression of microRNA-22 in neonatal rat cardiomyocytes increased cell size and induced hypertrophic markers, while the elimination of microRNA-22 attenuated hypertrophy induced by phenylephrine, isoprenaline or angiotensin II *(Figure 3 and Table 1)*.[26]

Another microRNA that has been associated with cardiac hypertrophy is microRNA-200c. MicroRNA-200c is a microRNA considered pro-hypertrophic. MicroRNA-200c is thought to be able to inhibit the action of myosin light chain kinase (MLCK). These two molecules have been shown to maintain a negative correlation in their concentrations. It means that overexpression of microRNA-200c reduces MLCK concentrations, and overexpression of microRNA-200c significantly increases the production of reactive oxygen species and apoptosis *(Figure 3 and Table 1)*.[4,27]

MicroRNA-185 is also a regulator of cardiac hypertrophy, and it plays an anti-hypertrophic role in the heart and has three major targets during the process such as Ncx1 (sodium/calcium transporter), Nfatc3 (nuclear factor activating T cells), and Camk2d (Ca2 +/Calmodulin-dependent protein kinase II) *(Figure 2 and Table 1)*.[25,28]

MicroRNA-378 is expressed in cardiac myocytes and not in cardiac fibroblasts, and it acts as a repressor of cardiac hypertrophy since it represses the pro-hypertrophic signal through the mitogen-activated protein kinase (MLCK) pathway when targeting MAPK1, to insulin-like growth factor receptor 1 (IGF1r), to Growth factor receptor-bound protein 2 (GRB2), and the Ras 1 kinase suppressor (Ksr1).[25,29] The overexpression of microRNA-378 blocks the activity of Ras, stimulated by phenylephrine and also prevents the activation of two signaling pathways, phosphatidylinositol 3 kinase (PI3K)/protein kinase B (AKT) and Raf1-mitogen-activated protein kinase kinase-1 (MEK1)-Extracellular signal-regulated protein kinase-1(ERK1)/2 *(Figure 3 and Table 1)*.[25,30]

CONCLUSION

MicroRNAs have become a research objective in recent decades not only regarding heart failure but for a wide range of pathologies because the pathways in which they can intervene are increasingly known. However, in order to become more useful in the clinic, it is important to know not only their function but also to know how they interact with other molecules, how they behave in circulation and in tissues, or to know if plasma concentrations are related to expressions at the tissue level. It is even possible that the concentration of one but of several microRNAs give us more information about the prognosis or diagnosis in

the future. MicroRNAs must be thought of not only at the individual level but as a large group of molecules that modify normal molecular pathways in response to disease.

As there are various pathophysiological mechanisms in the heart, there is a wide variety of microRNAs that alter their plasma or tissue levels. However, few will have clinical use in the future. It is because, at the moment, many of the alterations in the concentration or expression of the microRNAs have not reached a greater sensitivity or specificity to the traditional markers of heart failure. It is necessary to continue with microRNA research to give them a clear clinical utility and superior to current diagnostic and prognostic methods.

For the moment, it would be pertinent to carry out multicenter studies with a great variety of individuals since many of the studies that were presented above have been carried out in Anglo-Saxon countries, and few have been carried out in developing countries. Due to the genetic variants that could exist between populations, the studies could be adapted to the context in Mexico. For this, both private initiatives and public institutions have resources for microRNA research to benefit the population.

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