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Pleiotropic Effects of MicroRNA in Health and Disease

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ABSTRACT

MiRNAs are small, 19-25 nucleotides long strands of RNA that are non-coding and control the effects of messenger RNA. With more than 30.000 miRNAs, their roles are extensive. Since their discovery, it has been demonstrated that they are key elements in many important cellular functions, such as homeostasis, metabolism, development, and senescence. Due to rapid scientific progress, the role of miRNAs and the impact of their dysregulation on major human pathologies are being progressively recognized. Increasing evidence suggests their importance in medicine as potential biomarkers for diagnosis, prognosis, and therapy responsiveness, as well as potential therapeutic targets, making them potentially useful tools for clinical practice. This paper aims to review some of the most important and newest miRNAs interrelation with cardiovascular, neurological, renal, autoimmune, hepatic, infectious diseases, and cancer.

1. Introduction

1.1 MicroRNAs

MicroRNAs (miRNAs) were first discovered in the '90s as products of the lin-4 and let-7 genes that control the development of Caenorhabditis Elegans (Lee, Feinbaum, & Ambros, 1993). In the 2000s, the let-7 gene and gene expressions were discovered in many species and since then, many miRNAs have been identified in mammals (Lee, Feinbaum, & Ambros, 1993; Pasquinelli et al., 2000; Ardekani & Naeini, 2010).

MiRNAs are non-coding, 19-25 nucleotides (nt) long RNAs that control the stability and translation of messenger RNA (mRNA) through the interaction of nucleotides 2-8 from the 5' untranslated region (UTR) of the miRNA with the 3' UTR of the mRNA, named miRNA response element (MRE) (Heydarzadeh, Ranjbar, Karimi, Seif, & Alivand, 2021; Nejad, Stunden, & Gantier, 2018). However, miRNAs can interact through other non-canonical regions with mRNA and the MRE can be detected in regions other than the 3' UTR of the mRNA (Nejad, Stunden, & Gantier, 2018).

The biogenesis of miRNA begins with the transcription of a specific gene by RNA polymerase II and results in a primary stem-loop miRNA (pri-miRNA). Then the pri-miRNA is cleaved by the complex of Drosha and DGCR8 and a ~70 nt hairpin structured precursor (pre-miRNA) is produced (Bartel, 2004; Nejad, Stunden, & Gantier, 2018; Winter, Jung, Keller, Gregory, & Diederichs, 2009). The development of mature miRNAs is mediated by RNase III in the cytoplasm and then by association with Argonaute protein to create the RNA-induced silencing complex (RISC) (Heydarzadeh et al., 2021; Kim, Kim, & Kim, 2016; Wahid, Shehzad, Khan, & Kim, 2010).

In October 2018, the miRNA database reached 38.589 entries of both pre-miRNA and mature miRNA in several species (miRBase, 2021). The miRNAs have an important impact on the biological processes of organisms, such as apoptosis, metabolism (Lv et al., 2015; Ebert & Sharp, 2012), and signal transduction (Mitchelson, 2015). As demonstrated by experimental and clinical data their dysregulation is a cause or effect of many pathological processes, such as autoimmune disorders (Zhang, Wu, Zhao, & Lu, 2020),

diabetes (Li, 2014), cardiovascular disease (Siasos et al., 2020), infectious diseases (Tribolet et al., 2020) and cancer (Markopoulos et al., 2017; Xu, Zhang, Lv, & Zhu, 2015), to name a few. (figure 1) (table 1)

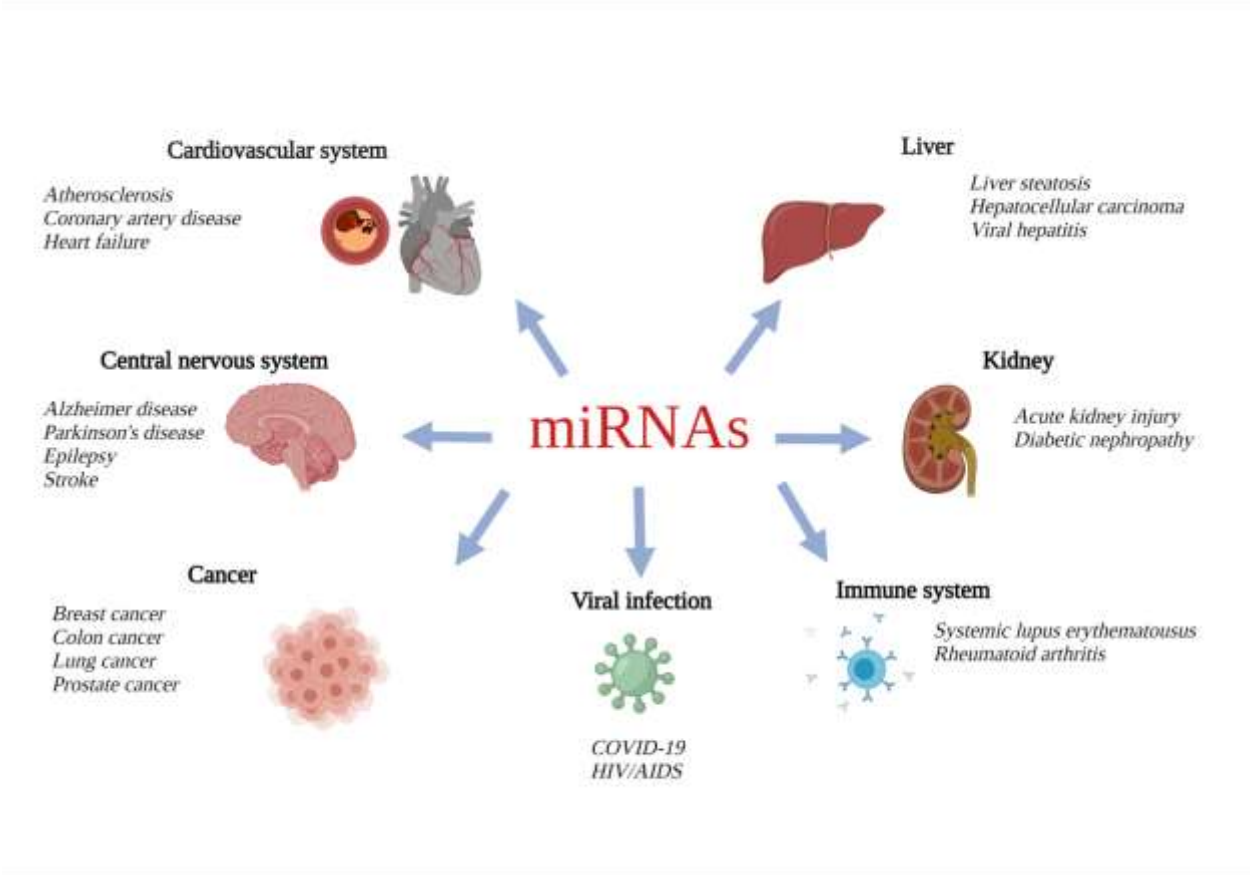

Figure 1. Pleiotropic effects of miRNAs in various pathologies

Table 1. Summary of miRNAs implicated in various pathologies

	Disease	MiRNAs implicated	References
Cardiovascular	CAD	miRNA-126-5p	Li, 2016
		miRNA-17, -92, -145, -155, -133, -208a	Fichtlscherer, 2010
		miRNA-133	Wang, 2013
		miRNA-31, -720	Wang, 2014
		miRNA-34a, -21, -30a, -106b	Han, 2015
		miRNA-24, -33, -103a, -122	Dong, 2017
	ACS/MI	miRNA-19a	Zhong, 2014
		miRNA-208a	Białek, 2015
		miRNA-21, -25, -92a, -106b, -126, -590-5p	Ren, 2013
		miRNA-19, -21, -122, -146, -155	Diel, 2012
		miRNA-122, -720, -140-3p, -2861, -3149	Li, Yang, 2015
	HF	miRNA-26a-5p, -145-3p, 485-3p, -487b-3p, -150-5p	Scrutinio, 2017
		miRNA-499, -401	Corsten, 2010
		miRNA-18b, -423-5p, -622, -129-5p, -645-3p, -1254	Tijsen, 2010
		miRNA-21	Zhang, 2017
Neurological	Ischemic stroke	miRNA-146a	Li, 2017; Li, Su, 2015

	IH	miRNA-146a	Zhu, 2015
	TBI	miRNA-146a	Ma, 2019
	Spinal injury	miRNA-146a	Paim, 2019
	Epilepsy	miRNA-146a	Aronica, 2010; Roncon , 2015
	Alzheimer's	miRNA-146a, -26b, -107, -30e, -34a, -125b, -200c, -34c, -425	Swarbrick, 2019
	Parkinson's	miRNA-146a	Caggiu, 2018
Renal	AKI	miRNA-24	Lorenzen, 2014
		miRNA-687	Bhatt, 2015
		miRNa-494	Lan, 2012
		miRNA-126, -127	Aguado-Fraile, 2012; Bruin, 2014
	DN	miRNA-192	Kato, 2007
		miRNA-21	Chau, 2012
Hepatic	HCC	miRNA-122	Bandiera, 2015; Szabo, 2013
		miRNA-192	Gu, 2019
		miRNA-21	Pan, Wang, 2010; Selaru, 2009; Tomimaru, 2012; Zhou, 2011
	NASH	miRNA-122	Cheung, 2008; Pirola, 2015
		miRNA-192	Pirola, 2015
		miRNA-21	Cheung, 2008; Loyer, 2016; Wu, 2016
	Steatosis	miRNA-192	Pirola, 2015
	Viral hepatitis	miRNA-122	Liang, 2016; Sarnow, 2016; Wang, Qiu, 2012
Viral infections	COVID-19	miRNA-16-2-3p, -183-5p	Li, 2020
		miRNA-3605-3p, -146a-5p, -142-3p, -21-5p	Tang, 2020
		miRNA-15b-5p, -486-5p, -486-3p, -31-5p, -99a-5p, -181a-2-3p	Tang, 2020
	HIV/AIDS	miRNA-223, -29a	Yahyaei, 2016
		miRNA-3162-3p	Huang, 2018
		miRNA-20b-5p, -195-5p, -16-5p, -223-3p	Biswas, 2019
Autoimmune disease	SLE	miRNA-146	Tang, 2009
		miRNA-155	Davis, 2014; Wang, Hou, 2010
		miRNA-21, -148a	Pan, 2010
		miRNA-150	Zhou, 2013
	RA	miRNA-338-5p	Guo, 2018
		miRNA-708-5p	Wu, 2018
		miRNA-548a-3p	Wang, 2018
Cancer	Breast cancer	miRNA-21, -145, -155, -125b	Iorio, 2005

		miRNA-210, -221, let-7d	Volinia, 2010
	Colon cancer	miRNA-200c, -27b, -158a, -326	Kjersem, 2014; Toiyama, 2014
	Lung cancer	miRNA-660, -451, -140-5p, -92a, -28-3p, -30c	Bianchi, 2011
	Prostate cancer	miRNA-195, -26a, -144, -375	Bryant, 2012; Mahn, 2011; Nguyen, 2013

CAD= coronary artery disease; ACS= acute coronary syndrome; MI= myocardial infarction; HF= heart failure; IH= intracerebral hemorrhage; TBI= traumatic brain injury; AKI= acute kidney injury; DN= diabetic nephropathy; HCC= hepatocellular carcinoma; NASH= non-alcoholic steatohepatitis; HIV= human immunodeficiency virus; AIDS= acquired immunodeficiency syndrome; SLE= systemic lupus erythematosus; RA=rheumatoid arthritis.

2. MiRNA in cardiovascular diseases

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality worldwide, with a mean prevalence of 523 million cases and a mean mortality of 18.6 million deaths in 2019 (Roth et al, 2020). Out of the CVDs, coronary artery disease (CAD) is one of the most common with 126 million individuals affected in 2017 (Khan et al., 2020).

In atherosclerosis and CAD pathophysiology, miRNA-126-5p seems to play an important role, as proposed by Li et al, who reported that the downregulation of this miRNA is associated with plaque formation (Li et al., 2016)

One of the first studies that correlated CAD and miRNA demonstrated the down-regulation of miRNA-126, -17, -92, -145, and -155 and upregulation of miRNA-133 and miRNA-208a among patients with CAD (Fichtlscherer et al., 2010). MiRNA-133 was used by Wang et al. (2013) to differentiate CAD from non-CAD patients with higher predictability rather than demographical data (e.g. sex, age, smoking, hypertension, diabetes). In addition, Wang et al. (2014) observed lower levels of miRNA-31 and miRNA-720 in patients with CAD and proposed them as useful biomarkers. Han et al. (2015) revealed through their study higher levels of miRNA-34a, miRNA-21, miRNA-30a, and miRNA-106b in patients with CAD compared with control. Dong et al. (2017) suggested the use of a 4 miRNAs panel (miRNA-24, miRNA-33, miRNA-103a, and miRNA-122) for the diagnosis of CAD.

In acute coronary syndromes (ACS) and myocardial infarction (MI), Zhong et al. (2014) mentioned the higher diagnostic value of miRNA-19a when compared to traditional biomarkers and Białek et al. (2015) referred that miRNA-208a reached peak concentrations earlier than traditional biomarkers, such as CK-MB, making it a useful biomarker. MiRNA-21, -25, -92a, -106b, -126, -451 and -590-5p were proposed to differentiate between ACS and non-ACS patients (Ren et al., 2013) and Diel et al. (2012) reported miRNA-19, -21, -122, -146 and -155 as useful in distinguishing patients with ACS and CAD. Li, Yang et al. (2015) demonstrated higher expression of circulating miRNA-122, -720, -140-3p, -2861, and -3149 in ACS patients and proposed this panel as having a higher diagnostic precision than each miRNA alone.

In heart failure (HF), miRNA-26a-5p, -145-3p, -485-3p, and -487b-3p were notably dysregulated, along with miRNA-150-5p, which plays a special role, as it is seriously downregulated in acute HF and moderately in chronic HF (Scrutinio et al., 2017). For acute HF, Corsten et al. (2010) proposed the use of miRNA-499 and miRNA-401 as biomarkers, since they are related to myocardial function and hepatic venous congestion. Tijsen et al. (2010) found the plasma level of miRNA-18b, -423-5p, -622, -129-5p, -645-3p, and -1254 to be elevated in HF patients compared with control, out of which miRNA-423-5p is most strongly correlated with HF. Levels of miRNA-423-5p are inversely correlated with the ejection fraction. MiRNA-21 is associated with CVD and Zhang et al. (2017) demonstrated high circulating levels of this miRNA subtype in patients with HF and, in addition, it is also correlated with the ejection fraction and BNP.

3. MiRNA in neurological diseases

Concerning the nervous system, miRNAs are now considered important regulators in the physiology of the synapse, as well as, in higher cognitive functions as learning and memory and they have also been involved in neurological disorders such as Alzheimer's and Parkinson's (Bonhoeffer & Yuste, 2002; Nelson & Keller, 2007; Shafi, Aliya, & Munshi, 2010). MiRNA-146a seems to have a pivotal role in neurological disorders as it is the most abundant in the central nervous system (CNS) (Fan et al., 2020). It can be found in neurons, astrocytes, and microglial cells with the main function of inflammation regulation through the nuclear factor kappa-B (NF-kB) pathway (Taganov, Boldin, Chang, & Baltimore, 2006).

MiRNA-146a was shown to have elevated levels in subacute ischemic stroke and low levels in acute ischemic stroke and intracerebral hemorrhage (Hu, Wang, Huang, Wang, & Zhang, 2018; Li et al., 2017; Li, Su, & Liu, 2015; Zhu, Wang, He, Jin, & Tang, 2015). In traumatic brain injury (TBI), its plasma levels are increased, however, in spinal injury miRNA-146a levels are decreased when compared to control groups (Ma, Xu, He, Li, & Luo, 2019; Paim et al., 2019). MiRNA-146a levels are upregulated in the plasma

of epileptic patients and the hippocampi of patients with temporal lobe epilepsy (Aronica et al., 2010; Roncon et al., 2015). Moreover, intranasal administration of miRNA-146a in a temporal lobe epilepsy mouse model attenuates neuroinflammation and the acute phase of the seizures (Tao et al., 2017).

In Alzheimer's and Parkinosn's neurodegenerative diseases the sera of patients were discovered to have low levels of miRNA-146a (Caggiu et al., 2018; Swarbrick, Wragg, Ghosh, & Stolzing, 2019). In Alzheimer's disease, along with miRNA-146a, other 9 miRNA (miRNA-26b, -107, -30e, -34a, -125b, -200c, -210, -34c, and -425) appeared to be dysregulated and this panel could potentially early diagnose Alzheimer's disease many years before the onset of symptoms (Swarbrick, Wragg, Ghosh, & Stolzing, 2019). Furthermore, the hippocampal levels of miRNA-146a can vary according to the Braak stage of the disease. As such they are increased in stages III and IV and decreased in stage VI (Müller, Kuiperij, Claassen, Küsters, & Verbeek, 2014).

4. MiRNA in renal diseases

Acute kidney injury (AKI) is defined by the quick decline in kidney function resulting in increased serum creatinine and/or decreased urinary output, caused by toxic and/or ischemic harm on the renal tubular cells (Bhatt K, Kato M, & Natarajan, 2016; Ronco, Bellomo, & Kellum, 2019). MiRNAs play a critical role in numerous pathophysiological mechanisms that result in AKI (Wei, Mi, & Dong, 2013). Lorenzen et al. (2014) discovered increased levels of miRNA-24 in murine kidneys that suffered an ischemia-reperfusion injury and silencing this miRNA resulted in renoprotective effects. MiRNA-687 is also considered to have a role in ischemia-reperfusion renal injury (Bhatt et al., 2015). Lan et al. (2012) demonstrated in mouse models that increased renal levels of miRNA-494 were associated with increased renal injury and that urinary levels of this miRNA were increased before any elevation of serum creatinine. Moreover, in humans, urinary levels of miRNA-494 were over 60-fold increased in patients with AKI when compared with control groups (Lan et al., 2012). MiRNA-126 and -127 were found to be renoprotective during ischemic renal injury through preservation of microvascular integrity (Aguado-Fraile et al., 2012; Bruin et al., 2014).

Diabetic nephropathy (DN) is a common complication of diabetes that can progress to end-stage kidney disease (Bhatt K, Kato M, & Natarajan, 2016). Transforming growth factor β1 (TGF-β1) is important in DN pathophysiology and leads to fibrosis and hypertrophy in renal cells via stimulation of extracellular matrix biogenesis (Chen, Jim, & Ziyadeh, 2003; Yamamoto, Nakamura, Noble, Ruoslahti, & Border, 1993). In a murine model, TGF-β1 also upregulates miRNA-192 levels in kidneys, which in turn upregulates extracellular matrix and fibrotic collagen (Kato et al., 2007). In contrast, Wang, Herman-Edelstein et al. (2010) reveal that miRNA-192 levels appear to be independent of TGF-β1 and that their effects are mediated through E-cadherin, not through extracellular matrix proteins. Also, miRNA-21 promotes fibrosis and endothelial damage in kidneys as demonstrated by Chau et al. (2012) in their study.

5. MiRNA in liver diseases

The most abundant and organ-specific miRNA in the liver is miRNA-122 and it represents approximately 52% of the hepatic miRNAs and insignificant expression in other cells and tissue types (Girard et al., 2008; Wang, He, Mackowiak, & Gao, 2021). MiRNA-194/192 have raised levels in the liver but are not specific, miRNA-29 is expressed in hepatic stellate cells (HSC) and miRNA-21 is the main miRNA in activated HSC (Caviglia et al., 2018).

Total miRNA production blockage in hepatocytes and miRNA-122 blockage produces similar pathologies such as liver steatosis and hepatocellular carcinoma (HCC) in murine models (Mattis et al., 2015; Sekine et al., 2009; Wang, He, Mackowiak, & Gao, 2021). Patients with HCC exhibit low levels of miARN-122 and this downregulation is associated with poor prognosis and metastasis (Bandiera et al., 2015; Szabo & Bala, 2013). Patients with non-alcoholic steatohepatitis (NASH) were discovered to have lower hepatic and higher plasma levels of miRNA-122 (Cheung et al., 2008; Pirola et al., 2015). With regard to the hepatitis B and C viruses (HCV and HBV), miRNA-122 pairs directly with the HCV RNA and promotes replication, whereas the same miRNA suppresses HBV replication. However, HBV can alter miRNA-122 physiology and progress to persistent infection and oncogenesis (Liang et al., 2016; Sarnow & Sagan, 2016; Wang, Qiu, et al., 2012).

MiRNA-192 was found by Gu et al. (2019) to be severely downregulated in hepatic cancer stem cells (CSC) and this alteration contributes to the HCC oncogenesis because miRNA-192 suppresses the CSC featured effects. Due to the anti oncogenic effects of miRNA-192/194, the administration of the two mentioned miRNAs could be a potential therapeutic target in HCC (Wang, He, Mackowiak, & Gao, 2021). MiRNA-192 was also discovered to have elevated levels in the plasma of patients with simple liver steatosis and NASH (Pirola et al., 2015).

MiRNA-29 expression in the hepatic microenvironment is remarkably downregulated in patients with hepatic fibrosis because the main role of this miRNA is to control the expression of the extracellular matrix (Roderburg et al., 2011). Administration of miRNA-29 improved liver fibrosis in murine models (Matsumoto et al., 2016). This miRNA subtype also has implications in glucose and lipid metabolism, as an expression of miRNA-29 reduces hyperglycaemic and insulin resistance responses in murine models by

reducing hepatic glucose production (Liang et al., 2013). On the other hand, hepatic triglyceride uptake is enhanced by inhibition of miRNA-29 in mice (Mattis et al., 2015). MiRNA-29 also has oncosupressive properties and is downregulated by alpha-fetoprotein (AFP) and it is downregulated in human HCC tissue and low levels are associated with poor prognosis (Parpart et al., 2014; Xiong et al., 2010).

MiRNA-21 promotes liver steatosis by promoting the secretion of very-low-density lipoprotein (VLDL) and inhibiting lipogenesis, thus it was discovered in very high levels in non-alcoholic fatty liver disease and NASH patients and mice (Calo et al., 2016; Cheung et al., 2008; Loyer et al., 2016; Vinciguerra et al., 2009; Wu et al., 2016). Elevated serum levels of this miRNA were also found by John et al. (2014) in patients with acute liver failure and by Song et al. (2010) in mice after partial hepatectomy. Also, miRNA-21 is considered an onco-miR that promotes HCC progression and its serum levels are considerably higher in HCC patients (Pan, Wang, & Wang, 2010; Selaru et al., 2009; Tomimaru et al., 2012; Zhou et al., 2011).

6. MiRNA in viral infectious diseases (COVID-19, HIV infection and AIDS)

On the 8th October 2021, the World Health Organisation (WHO) declared 236.599.025 confirmed cases of COVID-19 with 4.831.486 deaths worldwide (WHO, 2021). With this novel and serious pandemic, new roles of miRNA in COVID-19 are starting to emerge (Zhang et al., 2021). In his study, Li et al. (2020) specified 38 downregulated and 35 upregulated miRNAs, out of which miRNA-16-2-3p was most upregulated and miRNA-183-5p most downregulated. In another study, it was shown that miRNA-3605-3p was upregulated and miRNA-146a-5p, -142-3p, and -21-5p were downregulated (Tang et al., 2020). In addition, miRNA-15b-5p, -486-5p, and -486-3p were consistently upregulated and miRNA-31-5p, -99a-5p, and -181a-2-3p downregulated only in severe COVID-19 cases, proposing this panel of 6 miRNAs as predictors for the severity of the disease (Tang et al., 2020). Furthermore, Merino et al. (2020) discovered that the SARS-CoV-2 can produce up to 8 potential mature types of miRNA that can play a role in the pathophysiology of the disease. Liu et al. (2020) proposed in their study that SARS-CoV-2 viral miRNAs regulate the host's immune and inflammatory responses by altering key receptor responses in the immune system, inflammation-related proteins and by enhancing tumor necrosis factor α (TNFα).

Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) have a wide and serious impact that resulted in a multitude of studies, including miRNAs and their implications in these pathologies (Tribolet et al., 2020). In the study of Yahyaei et al. (2016) miRNA-223 and -29a were discovered to have elevated levels in the serum of patients who had repeated contact with the HIV but did not develop an infection and in the study of Huang et al. (2018), miRNA-3162-3p was found to be a great biomarker that differentiated early HIV infection (<1 year) from old infections (>1 year). Recently, Biswas et al. (2019) proposed a panel of miRNAs (miRNA-20b-5p, -195-5p, -16-5p, and -223-3p) as biomarkers for detecting early HIV infections that had 100% accuracy when compared to control groups.

7. MiRNA in autoimmune diseases

Autoimmune diseases are complex and chronic disorders that result from environmental factors and genetic variation (Zhang, Wu, Zhao, & Lu, 2020). There is a growing incidence of autoimmune disease patients with an important social impact (Roberts & Erdei, 2020; Yen & Singh, 2018).

Systemic lupus erythematosus (SLE) is a chronic autoimmune condition defined by the presence of autoantibodies directed against nuclear components and an excessive proinflammatory status (D'Cruz, Khamashta, & Hughes, 2007; Hong et al., 2020). Type I interferon plays an important role in the evolution of SLE (Banchereau & Pascual, 2006). MiRNA-146a is one of the negative regulators of inflammation via suppression of the NF-κB pathway (Taganov, Boldin, Chang, & Baltimore, 2006). It was discovered by Tang et al. (2009) that miRNA-146a was downregulated in peripheral blood mononuclear cells of patients with SLE and that this was responsible for stimulating type I IFN production. In turn, type I IFN contributes to the excessive inflammatory status through inhibition of miRNA-146a maturation (Qu et al., 2015). On the other hand, miRNA-155 can stimulate inflammation and type I IFN effects and it was demonstrated that downregulation attenuated cytokine production (Davis, Kis-Toth, & Tsokos, 2014; Wang, Hou, et al., 2010). MiRNA-21 and -148a were discovered by Pan et al. (2010) to be upregulated in CD4+ T cells and peripheral blood mononuclear cells in patients with SLE, which contributed to DNA alteration in T cells. Also, researchers demonstrated the correlation between miRNA-150 and chronicity scores in lupus nephritis and profibrotic gene expression in mesangial and proximal tubular cells (Zhou et al., 2013).

Rheumatoid arthritis (RA) is a systemic autoimmune disease defined by inflammatory and symmetrical distal joint destruction (Wang et al., 2020). Guo et al. (2018) demonstrated that miRNA-338-5p has implications in the proliferation, apoptosis, and migration of synoviocytes that are fibroblast-like. MiRNA-708-5p also has a role in fibroblast-like synoviocytes' apoptosis and can dampen the RA pathophysiological mechanisms (Wu, Fan, Ma, & Geng, 2018). MiRNA-548a-3p was proposed by Wang et al. (2018) as a promising biomarker and potential therapeutic target, as it regulates and reduces inflammation via the TLR4/NF-κB pathway.

8.. MiRNA in cancer and metastatic disease

Cancer is one of the leading causes worldwide of morbidity and mortality, with 19.292.789 new cases and 9.958.133 deaths in 2020 (Globocan, 2020). Scientific studies indicate that a majority of miRNA genes are found in genomic regions that are cancer-associated or fragile (Reddy, 2015). The implications of miRNAs were discovered in many types of cancer (e.g. breast, gastric, lung, colon) (Hao, He, Li, Wang, & Wang, 2017; Iorio et al., 2005; Michael, O' Connor, van Holst Pellekaan, Young, & James, 2003; Takamizawa et al., 2004). Much scientific data is pointing out the value of miRNAs as potential biomarkers in the prediction, diagnosis, and prognosis of oncological diseases (Reddy, 2015).

MiRNAs were classified in relation to cancer as "good, bad and ugly", where the "good" miRNAs are merely bystanders in oncogenesis, the "bad" are linked to tumorigenesis and the "ugly" are associated with destabilization of the tumoral cell and progression of the disease (Markopoulos et al, 2017; Voorhoeve & Agami, 2007).

Analysis of miRNAs in breast cancer tissues revealed that miRNA-21, -145, -155 and -125b could identify tumoral breast tissue versus normal tissue (Iorio et al., 2005). Furthermore, miRNA-210, -221, and let-7d appear to be downregulated in non-invasive ductal carcinoma and upregulated in invasive disease (Volinia et al., 2010), and miRNA-155 and -125b were correlated with responsiveness to therapy and prognosis (Sun et al., 2012; Wang, Tan, et al., 2012).

In colon cancer miRNA-200c, -27b, -158a, and -326 were revealed as useful biomarkers that could identify the metastatic disease (Kjersem et al., 2014; Toiyama et al., 2014). In lung cancer, a panel of miRNAs (miRNA-660, -451, -140-5p, -92a, -28-3p, -30c) were discovered to be dysregulated in the plasma of lung cancer patients 1-2 years prior to the diagnosis, making them useful predictors (Bianchi et al., 2011). In prostate cancer patients, the serum levels of miRNA-195 and -26a were significantly upregulated when compared to benign prostate hyperplasia (BPH) and miRNA-144 and -375 were found to be accurately correlated with the progression of the disease from localized to invasive or metastatic disease (Bryant et al., 2012; Mahn et al., 2011; Nguyen et al., 2013).

Some miRNAs can suppress and/or bypass cellular senescence and promote the growth of multiple cell types (Markopoulos et al., 2017). This is the case of the miRNA 17-92 cluster, also named oncomiR-1, and out of this cluster, miRNA-19 has been discovered to be a key regulator in oncogenic activity. This cluster is frequently upregulated in multiple oncologic diseases and was demonstrated to stimulate cell proliferation and to bypass apoptosis (Bischof & Martínez-Zamudio, 2015; Concepcion, Bonetti, & Ventura, 2012; Grillari, Hackl, Grillari-Voglauer, 2010; Mendell, 2008; Olive, Jiang, & He, 2010). Another central process of cancer progression is angiogenesis (Markopoulos et al., 2017). MiRNAs such as miRNA-27b, -130a, and let-7f are well-known proangiogenic factors, and miRNA-378 and the cluster of miRNA-17-92 have implications in tumoral angiogenesis (Urbich, Kuehbacher, & Dimmeler, 2008). Hypoxia-inducible factors stimulate the production of miRNA-210, which is an important modulator of angiogenesis in hypoxic conditions and vascular endothelial growth factor (VEGF) associated cell migration (Fasanaro et al., 2008; Markopoulos et al., 2017).

9. Conclusions

The experimental and clinical scientific data indicate the multiple implications of miRNAs in health and disease. The objective of this study is to highlight the important roles of miRNAs in many physiological processes such as homeostasis, senescence, and cell development, as well as in human pathologies, hence their potential for clinical use. The early detection of some diseases such as Alzheimer's and HIV infection could benefit from the study of miRNAs. They are also potential biomarkers that aid diagnosis in a number of cardiovascular pathologies and neurologic diseases. The assessment of the severity and prognosis of some diseases could also be improved since the intense study of miRNAs demonstrated their involvement in this area as well. In addition, miRNAs could also provide a new extensive range of possible therapeutic targets in some diseases such as epilepsy and hepatic pathologies. In cancer, the study of miRNAs could bring advantages in identification and diagnosis (e.g. lung cancer), prognosis (e.g. breast and prostate cancer) and offers new potential therapeutic arsenals or adjuncts. The main findings of this review are represented by various miRNA panels and roles that have implications in the mentioned pathologies discovered through literature research. The overall significance of the article is the attempt to systematize some of the representative scientific data on this topic, with the limitations given by the vast volume of information and scientific research regarding miRNAs.

The discovery of miRNAs almost two decades ago created a new and vast area of study in medicine. Convincing evidence emerges from the extensive scientific literature on miRNAs published in the last decade, creating wide perspectives for further studies and clinical applications, such as the inclusion of miRNAs in new disease diagnostic protocols or disease severity scores. MiRNAs assessment in clinical practice may pave the road to a modern, more in-depth, and personalized medicine.

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