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MiR-124 involvement of apoptosis, immunity and regulator of diseases

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Most microRNAs (miRNAs) are noncoding, conserved RNA molecules in vertebrates, and their roles are similar and very important. MiRNAs usually have tissue-specific expression, and abnormal levels of miRNAs have been associated with diseases and have been used as disease biomarkers. MiRNAs are widely involved in biological processes by regulating target mRNAs. MiR-124 is one of the best studied miRNAs in organisms. By targeting different mRNAs, miR-124 plays important roles in the central nervous system, cellular infiltration, pathophysiological processes of cardiovascular diseases, inflammation, immunity and tolerance, etc. This review mainly focuses on tissue-specific or abnormal expression of miR-124 as a biomarker and on the ways miR-124 for the treatment of serious diseases such as cancers.

Key words: miR-124, apoptosis, immune responses, diseases.

INTRODUCTION

MiRNAs are a group of noncoding, small, single-stranded RNA molecules that are approximately 19-25 nucleotides long and usually repress the expression of their target genes in multicellular organisms (Sharma, 2017; Hu and Zhang, 2019). MiRNAs are widely involved in biological processes by regulating target mRNAs and are also used as biomarkers of a number of diseases (Zhang et al., 2016; Komal et al., 2019; Mohammadi et al., 2019).

The first miRNA, lin-4, was discovered in 1993, and its roles were revealed to be involved in the larval development programs of the nematode *Caenorhabditis elegans* (Bartel, 2004; Sharma, 2017). Subsequently, a number of miRNAs have been found, and their roles have been characterized (Ramakrishna and Muddashetty, 2019; Shirjang et al., 2019). MiRNAs in humans and mice have been well studied, while the studies of miRNAs in lower vertebrates, such as fish, are just beginning. MiRNAs have been found in different fish, and their potent roles by targeting genes have been analyzed (Yang and He, 2014). It is well known that miRNAs are widely involved in biological functions through the regulation of target mRNAs (Ni et al., 2018; Zhang et al., 2016). The miRNA sequence and the binding site sequence on the 3' untranslated region (3′-UTR) of the mRNA are usually complementary (Li et al., 2013). Imperfect base pairing can lead to translational inhibition at the level of translation initiation and elongation of the target mRNA. However, it is demonstrated that miR-124

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can directly regulate multidrug resistance protein 4 (MRP4, ABCC4), and polymorphisms in the ABCC4 3'-UTR have no significant effect on miRNA regulation (Markova and Kroetz, 2014). It has been demonstrated that one miRNA usually has multiple target sites to target different genes in tissues to regulate different processes *in vivo*, and the miRNA can promote the degradation of the target mRNA or block its translation into protein, meanwhile one mRNA can also be targeted by multiple miRNAs (Sharma, 2017; Shirjang et al., 2019). In addition, long noncoding RNAs can also target miRNAs and regulate their expression (Shu et al., 2019).

MiRNAs are very important regulators of cellular mechanisms and physiological processes, such as cell cycle progression, cell division, apoptosis and necroptosis (Shirjang et al., 2019). To date, numbers of miRNAs have been discovered in different organisms, and diverse roles of these miRNAs have been described in physiological or pathological conditions (Mohammadi et al., 2019). It has been reported that humans have approximately 1000 miRNAs that can interfere with approximately 30% of gene expression, mostly as gene suppressors (Rassi et al., 2017). MiRNAs play crucial roles in the development and progression of human cancers, such as hepatocellular carcinoma (Lang and Ling, 2012). In brief, miRNAs can regulate nearly all cell signaling pathways from early development to cancer formation: differentiation, metabolism, proliferation, development, apoptotic cell death, viral infection and tumorigenesis (Ahir et al., 2017). Furthermore, miRNAs could be used to treat viral infections, such as hepatitis C virus infection (Thibault and Wilson, 2013).

A number of miRNAs are ubiquitously expressed in tissues, while they usually have tissue-specific expression. The functions of miRNAs and the relationships between miRNAs and mRNA were shown in Figure 1. MiR-124 is a member of the miRNA family and has common characteristics of miRNAs. Three pre-miR-124 variants (miR-124a or miR-124-1, miR-124-2 and miR-124-3) produce the same mature miRNA (He et al., 2016). MiR-124 is an evolutionarily conserved, noncoding microRNA in organisms. In humans and rats, miR-124 is most abundant in the brain, and many diseases of the brain are associated with abnormal levels of miR-124 (He et al., 2016; Taniguchi et al., 2015). Over the years, many studies have focused on the role of miR-124 in the nervous system (Wang et al., 2014; Sun et al., 2015), cardiovascular diseases (Bao et al., 2017), apoptosis (Han et al., 2019). The function of miR-124 in immune and inflammatory responses has been explored (Jin et al., 2017a, b). Studies have shown that miR-124 plays multiple roles in behavior, growth, immunity, signaling. MiR-124 can target neuronal genes to control behavior, immune genes to control inflammatory processes, and tumor-associated genes to affect tumors. This review mainly focuses on tissue-specific or abnormal expression of miR-124 as a biomarker and miR-124 for the treatment of serious diseases such as cancers.

MATERIALS AND METHODS

The information of this review was from journal articles published in Pumbed central database. Reviews "microRNA/miRNA", "miR-124", "miR-124, apoptosis", "miR-124, immune responses" and "miR-124, diseases" keywords in possible database were conducted in humans and animals.

RESULTS AND DISCUSSION

MiR-124 is a novel biomarker

The roles of miR-124 are usually associated with abundant expression in tissues. In humans, miR-124 is enriched in tissues including brain, liver, spinal cord, and neurons (Wang et al., 2014; Taniguchi et al., 2015; Zhao et al., 2015; Shaw et al., 2018), and its expression level can affect tumorigenesis, such as colorectal cancer (Taniguchi et al., 2015). Abnormal expression of miR-124 occurs in some diseases (Zeng et al., 2012). Therefore, miR-124 is known as a promising, novel biomarker of early diagnosis of diseases, especially cancers.

MiR-124 is involved in apoptosis and cell death

Recent studies have demonstrated that miR-124 is associated with apoptosis/cell death (Liang et al., 2017; Song et al., 2019). In rats, miR-124, which can be a biomarker of myocardial injury and infarction, regulates oxidative stress, cardiomyocyte apoptosis and myocardial infarction by targeting the gene Dhcr24 (Han et al., 2019). In cholangiocarcinoma cells, miR-124 can induce apoptotic cell death by targeting EZH2–STAT3 signaling (Ma et al., 2018). MiR-124 can silence polypyrimidine tract-binding protein 1 (PTB1) to cause drastic apoptosis of colon cancer cells (Taniguchi et al., 2015). The miR-124/AMPK/mTOR pathway can affect cell apoptosis (Gong et al., 2016). MiR-124 in glioma cells can inhibit cell growth and promote apoptosis (Wang et al., 2018). MiR-124 targeting Hic-5 can affect cell apoptosis after hypoxia damage in H9C2 cells (Jiang et al., 2018).

Roles of miR-124 in immune responses

Inflammation is a complicated cascade of reactions of the response of organisms to infections/injuries and is closely associated with various diseases (Lawrence et al., 2002). Classic inflammatory responses are induced by recognition receptors, such as Toll-like receptors (TLRs), which combine with the respective ligands to activate the innate immune system to release proinflammatory cytokines, including IL-1, IL-6, TNF-α, etc., resulting in the development of diverse inflammatory and autoimmune diseases (O'Shea and Murray, 2008; Wang and Xu 2017a, Wang et al., 2017b). However, detailed signaling pathways and regulatory mechanisms are not completely clear.

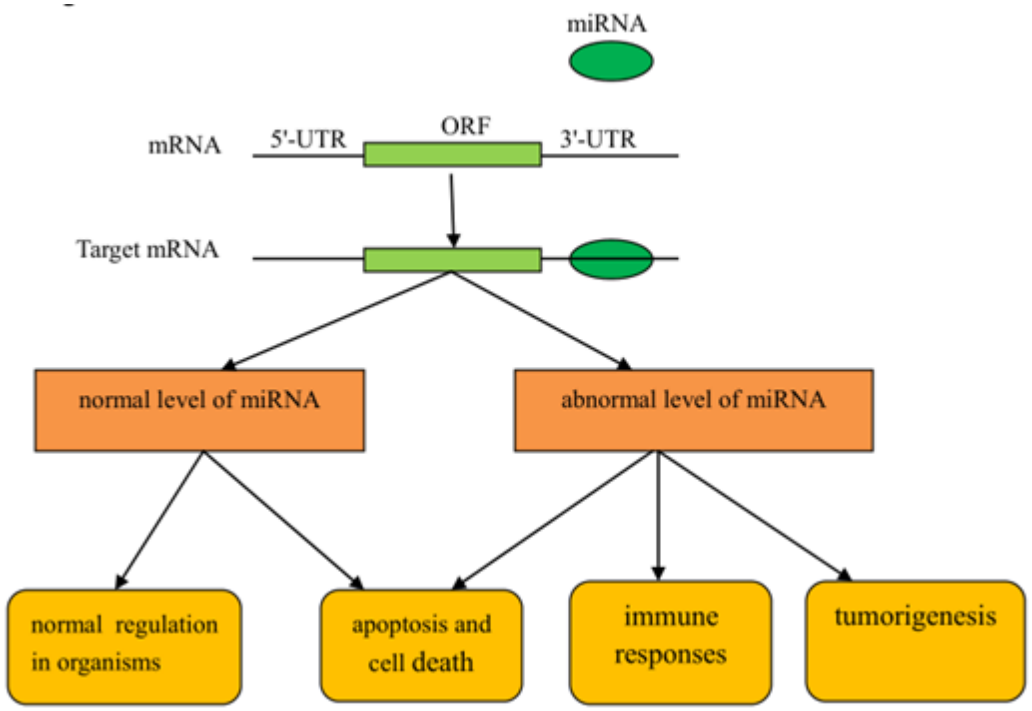

Figure 1. Relationship and the roles between miRNAs and mRNAs.

MiR-124 has been found to regulate various inflammatory processes. In mesenchymal stem cells, overexpressed miR-124 can upregulate IL-6 and STAT3 to improve the immunomodulatory capacity of the cells (Zhao et al., 2018). By inhibiting the expression of proinflammatory cytokines, miR-124 can mediate the cholinergic anti-inflammatory pathway (Sun et al., 2013). By targeting PPARγ, miR-124 can affect the production of proinflammatory cytokines in mice (Wang et al., 2017c). MiR-124 can reduce the activation of NF-κB (Li et al., 2013), and activated NF-κB can downregulate miR-124 (Wang et al., 2015). MiR-124 inhibits the mTOR signaling pathway and inhibits neuronal inflammation (Huang et al., 2018). MiR-124 in keratinocytes inhibits innate immune responses to all eviatechronic skin inflammation in atopic eczema (Yang et al., 2017). MiR-124 can activate peroxisome proliferator-activated receptor gamma (PPARγ) to regulate proinflammatory cytokine levels (Wang et al., 2017c). The level of miR-124 is decreased in lesion tissue of patients with atopic eczema and in keratinocytes response to inflammation factors that control chronic inflammatory processes, which suggests that miR-124 can alleviate chronic skin inflammation in atopic eczema by suppressing innate immune responses in keratinocytes (Yang et al., 2017). The miR-124-STAT3 pathway can partially regulate the immunomodulatory capacity of mesenchymal stem cells (Zhao et al., 2018). The expression of miR-124 can be induced during *Mycobacterium bovis* Bacillus Calmette–Guerin (BCG) infection in rats, and miR-124 is also able to regulate Toll-like receptor (TLR) signaling activity in RAW264.7 cells in response to BCG infection (Ma et al., 2014). MiR-124 downregulates the TLR signaling pathway during mycobacterial infection (Ma et al., 2014). Inhibition of miR-124 can activate the JNK and p38 pathways, which participate in the MAPK response to various stresses (Gong et al., 2019). MiR-124 in alveolar macrophages plays a role in the response to mycobacterial infection by negatively regulating TLR signaling genes (Ma et al., 2014). MiR-124 in human cells can induce mitochondrial apoptosis (Jin et al., 2017b).

MiR-124 is associated with some serious diseases

Various target genes of miR-124 have been associated with diverse diseases, including cancers. Abnormal expression of miR-124 in diverse cells usually occurs in cancers such as breast cancer and prostate cancer (Gu et al., 2016; Zhang et al., 2016; Liang et al., 2017), and miR-124 usually suppresses tumor formation, and its expression is downregulated in cancer patients (Zhang et al., 2015). Cancer is a malignant tumor, in which cells become unresponsive to inhibitory cellular growth signals and intrinsic cell replication limits, evade apoptotic signals, leading to tumorigenesis (Ahir et al., 2017).

As shown in Table 1, in humans, miR-124 targeting the PIK3CA gene can suppress cell proliferation in hepatocellular carcinoma (Lang and Ling, 2012), targeting HIPK3 can affect oncogenic properties of lung cancer

Table 1. Studies of miR-124 in some serious diseases.

Target	Diseases	References
PIK3CA	hepatocellular carcinoma	Lang and Ling, (2012)
HIPK3	lung cancer	Yu et al. (2018)
EphA2	glioma	Wu et al. (2018)
ITGA3	colorectal cancer	Sa et al. (2018)
RLIP76	malignant melanoma cells	Zhang et al. (2016)
Fra-2	glioma cells	Luo et al. (2018)
Toll-like receptor signaling	neuropathic pain	Grace et al. (2018)
K-ras mutation and NNK	lung tumorigenesis	Jin et al., (2017a)
PTPN1 signaling	Alzheimer's disease	Wang et al. (2018)
C/EBPα	hepatocellular carcinoma	Hu et al. (2019)
ZEB2	breast cancer	Ji et al. (2019)
DDX6/c-Myc/PTB1	colon cancer	Taniguchi et al. (2015)
Calpatn/CDK5 pathway proteins	Parkinson's disease	Kanagaraj et al. (2014)
SMYD3	Hepatitis C Virus	Zeng et al. (2012)
KITENIN	Colorectal Cancer	Park et al. (2014)
BACE1/-secretase	Alzheimer's disease	Fang et al. (2012)
STAT3	hepatocellular carcinoma	Lu et al. (2013)
ITGB3	endometriosis	Liu et al. (2019)

(Yu et al., 2018), targeting EphA2 can inhibit cell growth and motility in glioma (Wu et al., 2018), targeting integrin subunit alpha 3 (ITGA3) can be a potential target for the treatment of colorectal cancer (Sa et al., 2018), targeting gene RLIP76 can affect proliferation and invasion of malignant melanoma cells (Zhang et al., 2016), targeting Fra-2 suppresses glioma aggressiveness in glioma cells (Luo et al., 2018), and targeting Toll-like receptor signaling can be a valid strategy for reversing neuropathic pain (Grace et al., 2018). MiR-124 also inhibits lung tumorigenesis caused by K-ras mutation and NNK (Jin et al., 2017a). MiR-124 is involved in major depressive disorder (He et al., 2016; Fang et al., 2018). MiR-124 can suppress tumorigenesis in mice by silencing gene PTB1 (Taniguchi et al., 2015). MiR-124-PTPN1 signaling is a mediator that affects the synaptic and memory deficits in Alzheimer's disease (Wang et al., 2018). MiR-124 can improve brain repair in Parkinson's disease (Saraiva et al., 2016) etc. In addition, miR-124 has been associated with pancreatic cancer (Wang et al., 2014b), cervical cancer (Wilting et al., 2010), hematopoietic malignancies (Wong et al., 2011), leukemia (Chen et al., 2014), breast cancer (Ji et al., 2019), prostate cancer (Gu et al., 2016), etc.

Other functions

In addition to its involvement in apoptosis/cell death, immunity, and cancer, miR-124 is associated with fat metabolism, triglyceride homeostasis, stress response, and drug resistance (Fang et al., 2018; Shaw et al., 2018). In sheep, miR-124 is a crucial factor for adipogenesis (Pan et al., 2018). MiR-124 is also associated with neurite outgrowth in mammals (Yu et al., 2008; Su et al., 2019), miR-124 can also control drosophila behavior and neural development (Wang et al., 2014). In mice, miR-124 regulates the survival and differentiation of neural stem cells by regulating PAX3 (Wei et al., 2018). miR-124 is important in the response to various stresses, such as oxidative stress (Feng et al., 2017). MiR-124 is involved in the regulation of fatty acid and triglyceride homeostasis (Shaw et al., 2018). MiR-124 plays some roles in multidrug resistance (Popović et al., 2016; Liang et al., 2017).

In conclusion, MiRNAs, which are highly conserved and have a complex regulatory network in organisms, are important for regulating various biological responses to diverse environments. Abnormal levels of miRNAs would cause various diseases. MiR-124 is abundant in tissues and plays crucial roles in organisms. MiR-124 works *in vivo* by targeting various mRNAs and has multiple roles.MiR-124 can be involved in apoptosis, immunity and regulator of disease. More data are necessary to clarify the potential role and mechanisms of miR-124.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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