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A literature review on the role of miR-370 in disease☆

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ABSTRACT

MicroRNAs (miRNAs) are a class of small non-coding RNA molecules which regulate posttranscriptional events. Many studies have revealed that miRNAs have emerged as disease-suppressive molecules or oncomiRs by targeting disease oncogenes or suppressor genes. Therefore, miRNAs have become a hotspot in many researches. MiR-370 is located within the DLK1/DIO3 imprinting region on human chromosome 14. This region contains one of the largest miRNA clusters in the genome. Many miRNAs in this cluster including miR-370 have been reported to be involved in many diseases. The purpose of this review article is to summarize previous studies which have been published and have shown that miR-370 plays an important role in organ system diseases.

Contents

Abbreviations: AML, acute myeloid leukemia; BC, bladder cancer; CAD, coronary artery disease; CCA, cholangiocarcinoma; CDH13, cadherin 13; CML, chronic myeloid leukemia; Cpt1α, crinitine palmotoyl transferase 1α; CRC, colorectal cancer; Dnmt3a, DNA methyltransferase 3A; EMT, epithelial to mesenchymal transition; ENG, endoglin; Ets1, E26 oncogene homolog 1; FoxM1, forkhead box m1; FOXO1, forkhead box protein O1; GC, gastric cancer; GIST, gastrointestinal stromal tumors; HCC, hepatocellular carcinoma; IL-6, interleukin-6; IR, ischemia-reperfusion; IRS-1, insulin receptor substrate-1; LSCC, laryngeal squamous cell carcinoma; MAP3K8, kinase kinase kinase 8; MAPK, mitogen-activated protein kinase; MTC, medullary thyroid carcinoma; NF1, neurofibromatosis type 1; NF-KB, nuclear factor kappa B; NSCLC, non-small cell lung cancer; OA, osteoarthritis; OC, ovarian cancer; OSCC, oral squamous cell carcinoma; P21, p21WAF1/CIP1; PDGFRA, platelet-derived growth factor receptor, alpha polypeptide; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; RCC, renal cell carcinoma; SMO, smoothened; SOS1, son of sevenless homolog 1; TRAF4, tumor necrosis factor receptor-associated factor 4; TβRII, growth factor-β receptor II; UTR, untranslated region; VAMP-8, vesicle-associated membrane protein 8; WNT10B, wingless-type MMTV integration site family, member 10B; WT, Wilms' tumor; WTX, Wilms' tumor gene on the X-chromosome.

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Since the microRNA let-7 (Reinhart et al., 2000) and Lin-4 (Lee et al., 1993) were discovered for the first time, a growing number of microRNAs in multiple species have been found. Their function in the process of human physiology and pathology has been revealed step by step. MicroRNAs (miRNAs) are a class of small endogenous, non-coding RNAs that regulate gene expression at both the transcription and translation levels (Lagos-Quintana et al., 2001; Bartel, 2004; Pfeffer et al., 2004). MiRNAs can bind to the 3′-untranslated region (3′UTR) of the target mRNA and induce mRNA cleavage or translational repression. MiRNAs could take part in cell fate determination, proliferation, differentiation and cell death, with deregulation leading to aberrant gene expression in various diseases (Reinhart et al., 2000; Lewis et al., 2005). MiR-370 is one of the numerous microRNAs. It is located within the DLK1/DIO3 imprinting region on human chromosome 14. This region contains one of the largest miRNA clusters in the genome. Many miRNAs in this cluster including miR-370 have been reported to be involved in many organ system diseases (Suh et al., 2004; Haga and Phinney, 2012). The purpose of this review article is to summarize these studies which were recently published and have shown that miR-370 plays important roles in those diseases. (See Figs. 1– 10.)

1. In liver disease

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, especially in Asia (Lee et al., 2010; Alejandro et al., 2012; Zhang et al., 2012a). (Xu et al. (2013)found the involvement of a novel regulatory circuit consisting of miR-370, LIN28A, RelA/p65 and interleukin-6 (IL-6) in HCC progression. They discovered that miR-370 inhibits the malignant phenotype of HCC cells *in vitro*. Overexpression of miR-370 inhibits growth and metastasis of HCC cells *in vitro*. LIN28A was identified as a direct functional target of miR-370, which, in turn, blocks the biogenesis of miR-370 by binding to its precursor. RelA/p65 is the key subunit of the nuclear factor kappa B (NF-KB) family, which functions as an important promoter of liver carcinogenesis. IL-6, a well-known NF-KB downstream inflammatory molecule, reduced miR-370 but increased LIN28A levels in HCC. They suggest that early intervention to disrupt this loop may have therapeutic potential for HCC. Most cases of HCC arise in cirrhotic livers with persistent inflammation (Alejandro et al., 2012). Liver fibrosis is a main cause for chronic liver disease and can lead to HCC (Leung, 2005; Jahan et al., 2012), and miR-370 plays an inhibitory role in hepatic fibrogenesis by targeting smoothened (SMO), restoration of miR-370 may have beneficial effects in the treatment of liver fibrosis (Lu et al., 2015).

Hepatic ischemia–reperfusion (IR) injury is a major and inevitable problem occurring in the post-operative setting such as major liver resection and liver transplantation, which subsequently contributes to hepatic parenchymal cell injury and organ dysfunction (Peralta et al., 2013; Hou et al., 2014; Wang et al., 2015). Recent research found miR-370 acting via growth factor-β receptor II (TβRII) might play a potential role in hepatic ischemia–reperfusion (IR) injury, and inhibition of miR-370 efficiently attenuated the damage to the liver (Li et al., 2015).

2. In biliary disease

Cholangiocarcinoma (CCA) is the most common aggressive tumor of the biliary tract; it is the second most common primary hepatic malignancy accounting for 10%–20% of primary liver cancers (Khan et al., 2005; Razumilava and Gores, 2014). Interleukin-6 (IL-6) is a recognized mitogen and survival factor in human CCA and can contribute to tumor pathogenesis or progression and tumor growth by modulation of expression of miR-370, overexpression of IL-6 reduced miR-370 expression and reinstated MAP3K8 (kinase kinase kinase 8, a target of miR-370, and its expression was decreased in CCA) expression *in vitro* as well as in tumor cell xenografts *in vivo* (Meng et al., 2008). Meanwhile, WNT10B (wingless-type MMTV integration site family, member 10B) acts as a biologically relevant target by miR-370 in human CCA, and paternal allele of miR-370 is normally silenced through genomic imprinting and that the overexpression of IL-6 in CCA effectively suppressed the expression of miR-370 from the maternal allele (An et al., 2012).

3. In gynecological disease

Ovarian cancer (OC) is the seventh most lethal (in more developed areas) and eighth most lethal (in less developed areas) gynecologic malignancy worldwide (Lopez et al., 2012; Torre et al., 2015). Despite advances in diagnosis and chemotherapies, only approximately 30% of patients with advanced-stage ovarian cancer survive 5 years after their initial diagnosis (T et al., 2001). Some studies have identified both up-regulated and down-regulated miRNAs in ovarian carcinoma. Lee et al. (2012)found that four miRNAs (miR-30c, miR-30d, miR-30e-3p and miR-370) were significantly different between ovarian carcinomas and benign ovarian tissues, and expression of miR-370 was higher in stage I/II compared to stage III/IV samples and concerns to early clinical stage. Also, they identified miR-370 targeting CDH13. Epithelial to mesenchymal transition (EMT) is a process of cellular transdifferentiation by which epithelial cells lose their polarity and cell–cell contacts, reorganize their cytoskeleton, acquire the expression of mesenchymal markers and manifest a migratory phenotype. EMT has been categorized into 3 types—developmental (type I), fibrosis and wound healing (type II) and cancer (type III) (Lamouille and Derynck, 2007; Kalluri and Weinberg, 2009; Nieto, 2011). EMT is a decisive step towards tumor cell invasion and metastasis, and is positively correlated with poor patient prognosis (Hugo et al., 2007). MiR-370 was a key regulator of EMT-associated miRNA in ovarian cancer and endometrial carcinosarcoma (Koutsaki et al., 2014), and miR-370 was overexpressed in ovarian cancer and endometrial carcinosarcoma (Castilla et al., 2011). Interestingly, distinct results (Chen et al., 2014b) confirmed miR-370 was down-regulated in endometrioid ovarian cancer cell lines, which suppresses endometrioid ovarian cancer proliferation both *in vitro* and *in vivo*, the tumor suppressor role of miR-370 was through the negative regulation of its direct target gene Endoglin (ENG, also known as CD105).

The other recently researched function of miR-370 in the gynecologic setting was that of miR-370 in steroidogenic cells of ovary, which is likely to play a key role in posttranscriptional/posttranslational regulation of steroidogenesis (Hu et al., 2013).

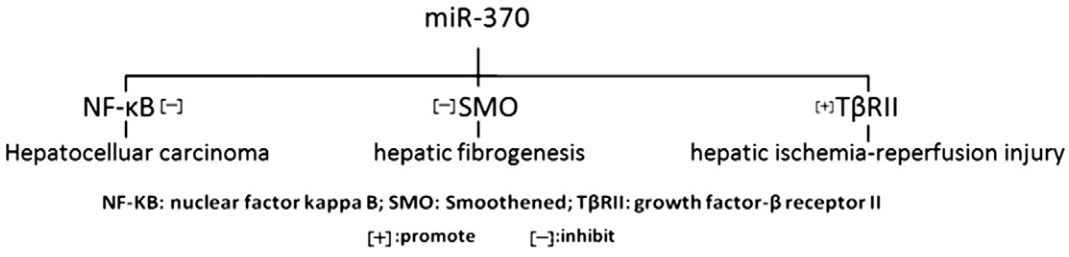

Fig. 1. Current knowledge of miR-370 in liver disease and its targets.