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REVIEW ARTICLE

LncRNA KCNQ1OT1: Molecular mechanisms and pathogenic roles in human diseases

Fangqi Xia [a], Yaqi Wang [a], Mengzhen Xue [a], Leiqi Zhu [a], Dengke Jia [a], Yue Shi [a], Yan Gao [a], Luoying Li [a], Yuanyang Li [a], Silong Chen [a], Guangfu Xu [a], Ding Yuan [a,b,*], Chengfu Yuan [a,b,c,*]

[a] *College of Medical Science, China Three Gorges University, Yichang, Hubei 443002, PR China*
[b] *Third-Grade Pharmacological Laboratory on Chinese Medicine Approved by State Administration of Traditional Chinese Medicine, Medical College of China Three Gorges, Yichang, Hubei 443002, PR China*
[c] *Hubei Key Laboratory of Tumour Microenvironment and Immunotherapy, China Three Gorges University, Yichang, Hubei 443002, PR China*

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Abstract Long non-coding RNAs (lncRNAs) exhibit a length more than 200 nucleotides and they are characterized by non-coding RNAs (ncRNA) not encoded into proteins. Over the past few years, the role and development of lncRNAs have aroused the rising attention of researchers. To be specific, KCNQ1OT1, the KCNQ1 opposite strand/antisense transcript 1, is clearly classified as a regulatory ncRNA. KCNQ1OT1 is capable of interacting with miRNAs, RNAs and proteins, thereby affecting gene expression and various cell functions (e.g., cell proliferation, migration, epithelial—mesenchymal transition (EMT), apoptosis, viability, autophagy and inflammation). KCNQ1OT1 is dysregulated in a wide range of human diseases (e.g., cardiovascular disease, cancer, diabetes, osteoarthritis, osteoporosis and cataract), and it is speculated to act as a therapeutic target for treating various human diseases. On the whole, this review aims to explore the biological functions, underlying mechanisms and pathogenic roles of KCNQ1OT1 in human diseases.

* Corresponding author. College of Medical Science, China Three Gorges University, Yichang, Hubei 443002, PR China.
E-mail addresses: 1394262283@qq.com (D. Yuan), yuancf46@ctgu.edu.cn (C. Yuan).
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Introduction

It is generally known that there are genes coding for proteins and numerous non-coding RNA (ncRNA) in human genome.[1] In addition, long non-coding RNAs (lncRNAs) take up a significant proportion, which are originally considered transcriptional noise, whereas they have been suggested to exhibit important biological functions recently.[2,3] Under a growing number of sequencing experiments concentrating on RNA these years (e.g., high-throughput sequencing), lncRNAs have been considered vital regulators in diverse human diseases.[4,5]

LncRNA refers to a type of RNA without the ability to code protein. On the whole, it exerts its function by regulating gene expression. As reported in existing studies, lncRNAs primarily interact with miRNAs, mRNAs, DNAs and proteins, thereby participating in the regulation of epigenetic, transcription, post-transcription, translation and post-translational levels.[6,7] LncRNAs were reported to be involved in epigenetic regulation; they could exert an effect on molecular processes (e.g., gene imprinting, histone modification and chromatin dynamics).[8] As suggested from the studies on the transcription level, lncRNAs interact with enhancers, promoters and chromatin modification complexes.[9] In addition, lncRNAs could act as miRNA sources and inhibitory regulators at a post-transcriptional level.[7] Moreover, lncRNAs can impact the translation efficiency and progress at a translation level, and they are capable of participating in the protein modification at a post-translational level.[10] In brief, lncRNAs exhibit a wide range of regulatory functions and critically impact cellular functions. It is evidenced that the dysregulation of lncRNAs is related to human diseases, and lncRNAs is expected to be a target for treating human diseases.[11] Accordingly, the molecular mechanism and pathogenic role of lncRNAs in human diseases should be clarified.

It is recently evidenced that the expression of lncRNA KCNQ1OT1 is abnormal in various human diseases. For instance, the following aspects have been reported, including the up-regulation in myocardial infarction, atherosclerosis, myocardial ischemia/reperfusion, coronary heart disease, auricular fibrillation, cardiac insufficiency, stroke, colon cancer, breast cancer, prostate cancer, diabetic cardiomyopathy, diabetic nephropathy, diabetic retinopathy, diabetic corneal endothelial keratopathy, diabetic cataract, osteoarthritis and cataract, as well as the down-regulation in osteoporosis. Thus, a summary is conducted here for the types of diseases and biological function of KCNQ1OT1 in diverse human diseases (Table 1). Since many studies reported that silencing KCNQ1OT1 can facilitate disease progression, KCNQ1OT1 is considered a target for the disease treatment. However, the effect of this lncRNA KCNQ1OT1 in various human diseases remains not be summarized.

Discovery and characterization of lncRNA KCNQ1OT1

KCNQ1OT1 refers to a lncRNAs, as well as an antisense RNA expressed in the paternal line. It is located in the *KCNQ1* gene and involved in the regulation of the blotting of human 11p15.5 region (Fig. 1). It is evidenced that the KCNQ1OT1 was termed as LIT1 that could be expanded to over 80 kb.[12] KCNQ1OT1 was reported to be initially identified in domain 2, one of the domains in Beckwith-Wiedemann Syndrome (BWS) pivotal area.[13] Moreover, over 50% of patients exhibiting BWS are related to dysregulation of the biallelic KCNQ1OT1.[14]

KCNQ1OT1 mediates transcriptional gene silencing of chromosome domains by targeting them to different nuclear loci known to be abundant in heterochromatic mechanisms.[15,16] Besides, one study suggested that human KCNQ1OT1 interacts with chromatin, at least in part via its maximum 5′20 KB sequence. Furthermore, it has shown that lncRNA KCNQ1OT1 can silence cell growth by interacting with chromatin.[17]

LncRNA Kcnq1ot1 RNA is composed of a 5′methyl cap and polyadenylic acid tail. It exhibits a certain degree of stability, whereas its half-life is 3.4 h. Moreover, silencing by Kcnq1ot1 is not determined by the RNA interference pathway, and the Kcnq1ot1 might physically coat the chromatin that it silences.[18] The expression of lncRNA Kcnq1ot1 will be down-regulated by NF-Y and its CCAAT promoter jointly.[19] KCNQ1OT1 transcription can be facilitated by the direct binding of β-catenin to the promoter of KCNQ1OT1.[20] Accordingly, after the lncRNA exerts its regulating effect, its expression inactivation may be related to chromatin interaction and DNA methylation. Furthermore, the expression level of the lncRNA will be regulated by the nucleoprotein and splice variants.

Molecular mechanisms and pathogenic roles of lncRNA KCNQ1OT1 in human diseases

Cardio-cerebrovascular disease

Cardio-cerebrovascular disease (CVD), i.e., the general term of cardiovascular and cerebrovascular diseases, is recognized as a vital human disease. A survey on the burden of various diseases reported that the burden of cardiovascular and cerebrovascular disease is significantly high. Moreover, cerebrovascular and ischemic heart diseases have become the biggest burden for many families.[21] For this reason, early diagnostic markers and appropriate therapeutic interventions are of significance for CVD patients.

Recent researches indicated that KCNQ1OT1 may critically impact the initiation and progression of CVD. Vausort et al. initially evidenced that KCNQ1OT1 was involved in cardiac physiological and pathological regulation in 2014. These researchers used sequencing technology to measure the lncRNAs of healthy controls and myocardial infarction (MI) patients, and then drew a conclusion that the KCNQ1OT1 level of MI patients was higher than that of healthy controls ($P < 0.01$).[22] Subsequently, as reported by Wang et al., KCNQ1OT1 silencing inhibits RUNX3 methylation, which offers protection against cardiac microvascular endothelial cells (CMECs) injury and inflammatory response in acute MI (AMI). As indicated from the study above, KCNQ1OT1 may act as a promising target for the disease treatment.[23]

Table 1 The regulatory functions of KCNQ1OT1 in several human diseases.

Diseases	Type of diseases	Expression in diseases	Biological function	Related gene	Ref.
Cardio-cerebrovascular disease	Myocardial infarction (MI)	Up	Regulates cell activity and inflammation	RUNX3	[23]
	Atherosclerosis	Up	Increases lipid accumulation and promotes atherosclerosis	miR-452-3p, HDAC3, ABCA1	[25]
	Myocardial ischemia/reperfusion	Up	Modulate myocardial ischemia reperfusion injury in mice	microRNA-204-5p, LGALS3	[26]
		Up	Low expression of KCNQ1OT1 defends ischemia/reperfusion injury	AdipoR1, p38 MAPK, NF-κB	[27]
	Coronary artery disease	Up	A novel diagnostic marker for coronary artery disease	—	[29]
	Atrial fibrillation	Up	Regulates atrial fibrillation	miR-384b, CACNA1C	[28]
	Heart failure	Up	Accelerates cardiomyocyte apoptosis	FUS	[30]
	Ischemic stroke	Up	Facilitates autophagy and promotes cell viability	miR-200a, FOXO3, ATG7	[32]
Cancer	Colon cancer	Up	Increases the chemical resistance	miR-34a, ATG4B	[43]
		Up	Common diagnostic biomarkers	miR-484, ANKRD36	[45]
		Up	Predict survival of colon adenocarcinoma		[44]
	Breast cancer	Up	Impairs cell function in breast cancer	has-miR-107	[38]
		Up	Promotes the occurrence and development of breast cancer cell tumors	miR-145, CCNE2	[37]
		Up	Gives rise to the tumor progression	DNMT1, PTEN	[39]
	Prostate cancer	Up	Facilitates immune escape and accelerates the deterioration in prostate cancer	—	[36]
Diabetes	Diabetic cardiomyopathy	Up	Low expression of KCNQ1OT1 reduces pyroptosis and fibrosis	miR-214-3p, caspase-1	[51]
		Up	Mediates pyroptosis in diabetic cardiomyopathy	miR-214-3p, caspase-1	[52]
	Diabetic nephropathy	Up	Knocking down KCNQ1OT1 reduces oxidative stress and cell apoptosis	miR-506-3p	[54]
		Up	Regulates proliferation, pyroptosis and fibrosis of diabetic nephropathy cells	miR-18b-5p, SORBS2	[55]
		Up	Regulates cell proliferation, oxidative stress and extracellular matrix accumulation	miR-18b, HMGA2	[56]
	Diabetic retinopathy	Up	Regulates the development of diabetic retinopathy	miR-1470, EGFR	[58]
	Diabetic corneal endothelial keratopathy	Up	Accelerates cell apoptosis	miR-214, caspase-1	[59]
	Diabetic cataract	Up	Low expression of KCNQ1OT1 restrains cell activity, migration and	miR-26a-5p, ITGAV, TGF-β, Smad3	[60]

Table 1 (*continued*)

Diseases	Type of diseases	Expression in diseases	Biological function	Related gene	Ref.
			epithelial—mesenchymal transition		
Other diseases	Osteoarthritis	—	Involving in the development of osteoarthritis	has-miR-1202, ETS1	69
	Osteoporosis	Down	promotes osteogenic differentiation and suppresses osteoclast differentiation	Bglap, Alp, Ctsk, Oscar	65
	cataract	Up	Promotes Cataractogenesis	miR-214, Caspase-1	71
		Up	Accelerates cell proliferation and epithelial —mesenchymal transition	SMAD4	72
		Up	regulates apoptosis of lens epithelial cells	miR-29c-3p, FOS	73

On the one hand, the results of a research suggested that the expression level of KCNQ1OT1 in atherosclerotic plaques is up-regulated.[24] On the other hand, as revealed by Yu et al., the mouse Kcnq1ot1 RNA can competitively bind miR-452-3p, which up-regulates the expression of HDAC3 and then down-regulates the expression of ABCA1. Lastly, they drew a conclusion that the mouse Kcnq1ot1 RNA is capable of promoting lipid accumulation in macrophages and accelerating the progression of atherosclerosis.[25] Thus, down-regulating the expression of KCNQ1OT1 may be an effective target to prevent and treat atherosclerotic cardiovascular disease.

Moreover, a study demonstrated that down-regulating KCNQ1OT1 could regulate the AdipoR1 and participate in p38 MAPK/NF-κB axis, which protected the myocardium from myocardial ischemia reperfusion (IR) injury after AMI.[26] As proved by another study, KCNQ1OT1 up-regulated LGALS3 by competitively binding miR-204-5p, which caused myocardial ischemia/reperfusion injury to be aggravated.[27] As indicated from the two mentioned studies, KCNQ1OT1 provides a new idea to treat myocardial IR injury.

In addition, Shen et al. reported that YY1 could up-regulate KCNQ1OT1 and impact the regulation of miR-384/CACNA1C signaling pathway; as a result, it could regulate angiotensin II-induced atrial fibrillation (AF).[28] Besides, an increase in KCNQ1OT1 was reported to indicate that coronary artery disease (CAD) and KCNQ1OT1 can be exploited as a novel biomarker for CAD.[29] In the end, Lei et al. reported that overexpression of KCNQ1OT1 will down-regulate the expression of FUS and facilitate the apoptosis of mouse cardiomyocyte, whereas the inhibition of KCNQ1OT1 will achieve the reverse results. Besides, the consistent results were achieved in the *in vivo* experiment. Lastly, it was concluded that KCNQ1OT1 can affect cardiomyocyte apoptosis in heart failure (HF).[30]

Stroke is considered the most common brain diseases, as well as one of the major causes of increased disability and mortality, in which ischemia accounts for approximately 80 percent.[31] According to Yu et al., silencing KCNQ1OT1 can significantly reduce the infarct volume and the neurological dysfunction in mice. Moreover, the underlying molecular mechanism is that silencing KCNQ1OT1 could enhance cell viability and suppress autophagy attributed to ischemia and

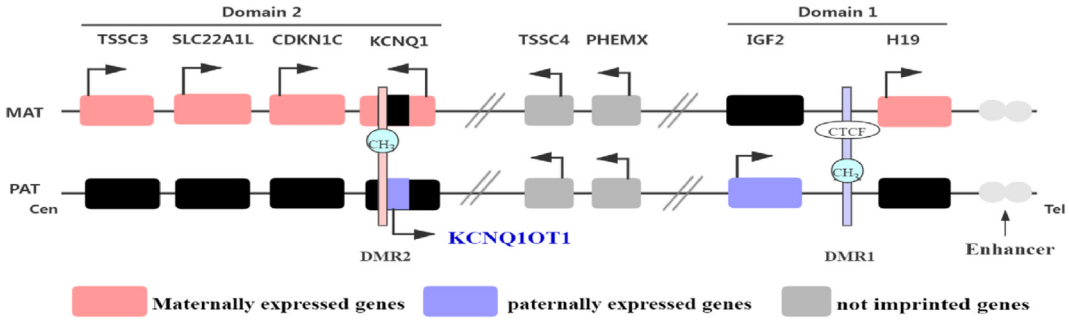

Figure 1 Map of the 11p15 imprinted area. The direction of transcription is indicated by a square arrow. The hatched line indicates the 11p15 area that is not shown. The positions of DMR1 and DMR2 are represented by light blue and pink boxes, respectively. Methylation is represented by a circle containing methyl (CH_3). Cen, centromere; Tel, telomere.

reperfusion by participating in the miR-200a/FOXO3/ATG7 signal axis.[32]

Cancer

Cancer is suggested to primarily account for the increase in mortality in the world's population, with lung cancer, colorectal cancer, breast cancer and prostate cancer showing the largest incidence rates.[33] It is generally accepted that the incidence of cancer continues to increase.[34] However, the causes of most cancers (e.g., prostate cancer, colon cancer and breast cancer) remain unclear.[35] Thus, the vital factors and the molecular mechanisms involved in the mentioned cancer regulation should be determined.

According to numerous recent studies, KCNQ1OT1 can expedite the progression of the mentioned cancers, and KCNQ1OT1 knockdown can inhibit the development of the mentioned cancers. Thus, KCNQ1OT1 is proven to critically impact the mentioned cancers.[36–45] For instance, KCNQ1OT1 can regulate the development of prostate cancer. Chen et al. reported that KCNQ1OT1 could competitively bind miR-15a and up-regulated PD-L1, thereby accelerating tumor escape. However, silencing of KCNQ1OT1 in prostate cancer cells produced the opposite effect. Lastly, they drew a conclusion that KCNQ1OT1 up-regulated PD-L1 by miR-15a sponge, resulting in facilitating immune escape and accelerating the deterioration in prostate cancer.[36]

Moreover, lncRNA KCNQ1OT1 can participate in the occurrence of breast tumors.[39] According to Feng et al., KCNQ1OT1 could regulate the occurrence and development of breast cancer tumors through the KCNQ1OT1/miR-145/CCNE2 signaling pathway, and this pathway had a vital regulatory effect on breast cancer.[37] A study indicated that silencing KCNQ1OT1 is capable of impairing the function of breast cancer cells. Moreover, the underlying molecular mechanism may result from the reverse regulation of hsa-miR-107 and the downstream target of KCNQ1OT1.[38] As demonstrated by another study, YY1 knockdown exerted a tumor suppressor effect on triple-negative breast cancer (TNBC), and the underlying molecular mechanism complied with the regulation of the mouse Kcnq1ot1/DNMT1/PTEN axis. This will provide support for further research on the anti-tumor treatment of TNBC.[40]

Furthermore, KCNQ1OT1 was proven to be potential a biomarker in colon adenocarcinoma.[41] Next, some findings revealed that KCNQ1OT1 might be a vital factor in predicting colon adenocarcinoma and an underlying target for treating colon adenocarcinoma.[42] In an existing study, KCNQ1OT1 was found to up-regulate Atg4B expression by competitively binding to miR-34a, which facilitated the chemical resistance in colon cancer. Besides, KCNQ1OT1 was suggested to be a potential treatment target for colon cancer.[43] In a secondary analysis among clinic pathological, genomic and survival data, overexpression of KCNQ1OT1 was suggested to probably be a meaningful standalone indicator for predicting shorter lifetimes and no recurrence in patients with colon adenocarcinoma.[44] In one recent research on lncRNAs, KCNQ1OT1 was identified as a conventional diagnostic marker for colon cancer occurrence and metastasis. Moreover, KCNQ1OT1 participated in the occurrence of colon cancer via the KCNQ1OT1/miR-484/ANKRD36 signaling pathway.[45] On the whole, as revealed from the mentioned studies, KCNQ1OT1 may be a biomarker to diagnose cancer, as well as a vital regulator to regulate cancer.

Diabetes

Diabetes is a group of metabolic disorders with high morbidity, the complications of which have increased substantially.[46,47] A survey on diabetes around the world proved that diabetes had become increasingly prevalent in the world, and in many countries, diabetes affected people's lives, increased the burden on society and increased the mortality rate of the country's population.[48] Furthermore, as suggested from statistics, many diabetic patients do not know their condition, so they are more likely to develop complications of diabetes. It is therefore suggested that novel regulatory factors should be found, and appropriate therapeutic interventions are required.

At the advanced stages of diabetes, patients often develop long-term vascular complications of diabetes, which roughly include microangiopathy caused by damage to small blood vessels, and macroangiopathy attributed to damaged arteries.[49] Diabetes is one of the universal diseases causing death, and cardiovascular disease refers to the critical complication of diabetes causing death.[50] According to one study by Fan et al., low expression of the mouse kcnq1ot1 could inhibit cardiomyocyte apoptosis and fibrosis. Subsequently, they reported that the mouse kcnq1ot1 participated in the regulation of the process of diabetic cardiomyopathy through the Kcnq1ot1/miR-214-3p/caspase-1/TGF-β1z axis.[51,52] And they proposed that KCNQ1OT1 might be a key regulator of DCM.

Diabetes has numerous complications, among which diabetic nephropathy (DN) is regarded as the most common occurrence in diabetic patients.[53] Recently, Fan et al. demonstrated that down-regulation of KCNQ1OT1 up-regulated the expression of miR-506-3p, thereby inhibiting the oxidative stress and pyrophosphorylation of HK-2 cells induced by high glucose.[54] Furthermore, Ran et al. demonstrated that KCNQ1OT1 can competitively bind miR-18b-5p and regulate the expression of SORBS2, which inhibits the NF-κB signaling pathway. Lastly, they concluded that KCNQ1OT1 could affect cell proliferation and apoptosis in DN.[55] Furthermore, Li et al. demonstrated that KCNQ1OT1 knockdown could down-regulate the expression of HMGA2 by up-regulating the expression of miR-18b. Moreover, they drew a conclusion that KCNQ1OT1 could affect the viability, oxidative capacity and the accumulation of extracellular matrix of human mesangial cells induced by high glucose.[56] The mentioned researches provided new insights into the treatment of DN.

It was reported that diabetic retinopathy (DR) was the most notable microvascular complication and the main cause of low vision and visual loss among people aged 15 to 64.[57] A recent study found that KCNQ1OT1 competitively bound to miR-1470 to regulate epidermal growth factor receptor (EGFR) in DR, which affected the progression of DR.[58] Other vital ocular manifestations of diabetes consist

of corneal endothelial keratopathy and cataract. It was reported that KCNQ1OT1 could sponge miR-214 to regulate the expression of caspase-1 and then regulate the development of diabetic corneal endothelial keratosis. Also, they proposed that KCNQ1OT1 might be a novel target to treat diabetic corneal endothelial keratopathy.[59] In addition, Liu et al. demonstrated that KCNQ1OT1 could competitively bind miR-26a-5p to regulate the expression of ITGAV, thereby affecting the TGF-β/Smad3 signaling pathway. They lastly proposed that silencing KCNQ1OT1 can inhibit the viability, migration and epithelial—mesenchymal transition (EMT) of lens epithelial cells.[60] Given the mentioned studies, KCNQ1OT1 was proven a vital biological indicator and a regulatory factor for diabetic patients.

Other diseases

Osteoporosis, characterized by the increased fragility of bone, is a major clinical problem in older women and men, which causes fractures.[61] Accordingly, it is important to find a novel treatment mechanism for the cause of osteoporosis. One study reported that KCNQ1OT1 acted as a competitive endogenous RNA to impact the miR-214/BMP2 signaling pathway, thereby enabling BMSCs to differentiate into more osteoblasts.[62] Subsequently, it was reported that bone marrow mesenchymal stem cells (BMSCs) had disordered osteogenic differentiation and senescence in the elderly, which made a considerable number of the elderly prone to osteoporosis.[63] In a high-throughput sequencing experiment, the most significantly downregulated expression of lncRNA in male osteoporosis were measured as KCNQ1OT1.[64] Furthermore, a previous research demonstrated that the mouse Kcnq1ot1 could promote osteogenic differentiation and reduce osteoclast differentiation.[65] As revealed from the mentioned studies, KCNQ1OT1 can be a therapeutic target against osteoporosis.

Osteoarthritis (OA) is one of the most common chronic diseases.[66] It is evidenced that OA occurs most frequently among all types of arthritis in the world.[67] In addition, OA is a serious human disease and some researchers considered OA a public health crisis.[68] Thus, there is an urgent need for osteoarthritis to develop a key factor to ensure patients receive safe and effective treatments. Recently, according to one competing endogenous RNA network analysis by Liu et al. in 2020, the interaction in the KCNQ1OT1-has-miR-1202-ETS1 signaling pathways was revealed. Moreover, they believed that this signaling pathway might affect the process of OA and was a key mechanism for regulating OA.[69]

Cataract is characterized by the opacity of the lens, and it is also the world's number one eye disease causing blindness.[70] With the growing population in society, cataract disease has been increasingly prominent. For this reason, a novel key regulator for cataract disease should be found. A study by Jin et al. in2017 showed that silencing KCNQ1OT1 could regulate the expression of miR-214, which in turn affected the expression of caspase-1. These researchers suggested that KCNQ1OT1 could regulate the cataract process via the KCNQ1OT1-miR-214-caspase-1 signaling pathway.[71] On the other hand, one study reported that KCNQ1OT could make lens epithelial cells proliferate and transformed lens epithelial cells into mesenchymal cells by regulating the expression of SMAD4 by Jin et al. in 2018. They also consider that the results of this research revealed a novel molecular mechanism for the progression of cataracts and created a vital regulator for the disease.[72] Lastly, as reported recently, KCNQ1OT1 participated in the development of cataracts by involving in the regulation of miR-29c-3p/FOS signaling pathway.[73]

The regulatory mechanisms of KCNQ1OT1

In recent years, lncRNA-microRNA-mRNA axis has been determined as a novel regulatory signal pathway and critically impacts a variety of clinical diseases.[74] To be specific, lncRNA, a competitive endogenous RNA (ceRNA), competitively binds to microRNA, which regulates its downstream targets.[75] Thus, lncRNA, acting as ceRNA, is considered to be the main mechanism of KCNQ1OT1 involved in the development of human diseases. First, it was reported that KCNQ1OT1 acts as a ceRNA and affects its downstream target caspase-1 by competitively binding miR-214-3p, which regulates the progression of diabetic cardiomyopathy and promotes the formation of cataracts.[51,52,71] Second, Yu et al. reported that the mouse kcnq1ot1 acted as ceRNA to regulate the function of miR-452-3p/HDAC3/ABCA1 signaling pathway, thereby promoting lipid deposition on the arterial wall and atherosclerosis.[25] It was reported that KCNQ1OT1 was employed as ceRNA to involve in regulating the KCNQ1OT1/microRNA-204-5p/LGALS3 axis, thereby affecting myocardial ischemia/reperfusion injury.[27] According to one study, KCNQ1OT1 was adopted as ceRNA to regulate the KCNQ1OT1/miR-384b/CACNA1C signaling pathway, thereby affecting atrial fibrillation.[28] KCNQ1OT1 was reported to act as ceRNA to involve in regulating KCNQ1OT1/miR-200a/FOXO3/ATG7 axis, thereby affecting autophagy in cerebral ischemic stroke.[32] KCNQ1OT1 was reported as ceRNA to regulate the KCNQ1OT1/miR-34a/Atg4B signaling pathway, thereby improving the chemical resistance.[43] KCNQ1OT1 was suggested as ceRNA to regulate the KCNQ1OT1/miR-181a-5p/PCGF2 signaling pathway, and then affected the progression of colon and rectal cancer.[45] KCNQ1OT1 acted as ceRNA to regulate the KCNQ1OT1/miR-145/CCNE2 axis, thus probably leading to breast cancer tumor genesis and progression.[37] Furthermore, it was reported that KCNQ1OT1 was employed as ceRNA to regulate KCNQ1OT1/miR-18b-5p/SORBS2 axis, which regulated diabetic nephropathy cells proliferation.[55] As indicated from a research report, KCNQ1OT1 was adopted as ceRNA to regulate miR-26a-5p/ITGAV/TGF-β/Smad3 axis, which affected the development of lens epithelial cells.[60] Lastly, according to one study, KCNQ1OT1 acted as ceRNA to regulate KCNQ1OT1/miR-29c-3p/FOS axis to regulate EMT, cell proliferation and facilitate apoptosis.[73]

In addition, KCNQ1OT1 is capable of regulating various pathways to affect other human diseases besides the role of competitively binding microRNA. For instance, it was reported that KCNQ1OT1 silencing inhibits Runt-related transcription factor (RUNX) 3 methylation, which protects against CMEC injury and inflammatory response in AMI.[23] Furthermore, KCNQ1OT1 was suggested to promote

cardiomyocyte apoptosis by regulating the expression of FUS in heart failure.[30] The mentioned findings reveal the complexity of the role of KCNQ1OT1, which helps intervene and treat the human diseases timely during the development of diseases.

Conclusion and perspectives

Recently, as numerous researches focused on KCNQ1OT1, the characteristics of KCNQ1OT involved in human diseases are increasingly clarified. On the one hand, KCNQ1OT1 is capable of impacting cell functions of various human diseases (e.g., proliferation, migration, EMT, apoptosis, viability, autophagy and inflammation). The mechanism of KCNQ1OT1 involved in disease regulation is significantly complex and involves numerous processes (e.g., competitively binding microRNAs, promoting RUNX3 methylation, regulating FUS expression and activating DNMT1/PTEN signaling pathways) (Fig. 2). On the other hand, KCNQ1OT1 may be regarded as novel biomarkers, and it can act as a meaningful independent prognostic biomarker of the length of survival and the presence or absence of recurrence. Besides, it may become a novel factor involved in the treatment of human diseases. Furthermore, what role the KCNQ1OT1 plays in nervous system diseases remains unclear.

In the present review, insights are gained into the complex mechanism of KCNQ1OT1 in a variety of human diseases, as well as its pathogenic role in various human diseases. Though some reports have been conducted on the role of KCNQ1OT1 in more human diseases, we have not summarized these reports. However, the human diseases described in this review are significantly common and important. To a certain extent, several human diseases in the review can reflect the effect of KCNQ1OT1 on human diseases, as well as the molecular mechanism of its action.

RNA degradation refers to a common activity, and ncRNA exhibiting a wide distribution is highly unstable and has different degradation mechanisms. Given a report by Milligan et al., as impacted by the functional redundancy between the components of the degradation mechanism, ncRNA was targeted by a variety of cofactors, and it was rapidly degraded.[76] Carroll et al. revealed that the recognition RNA binding proteins Nrd1 and Nab3 could critically impact the termination and degradation of the mentioned ncRNA transcripts.[77] In addition, Houseley et al. reported that Trf4 and exosomes could mediate the degradation of ncRNA transcripts.[78] Moreover, according to Xing et al., 3′—5′ exoribonuclease PNPT1 could trigger the degradation of poly(A) ncRNAs.[79] As mentioned earlier, Kcnq1ot1 RNA comprises a 5′methyl cap and polyadenylic acid tail. Thus, this study speculates that the Kcnq1ot1 will be degraded to a certain extent. However, whether KCNQ1OT1 will be degraded after its action is completed in the procession of human diseases should be verified in depth.

In terms of clinical application, the mentioned studies on KCNQ1OT1 have not fully clarified its role, and several vital issues in its clinical application remain to be resolved. In brief, KCNQ1OT1 acts as a vital factor involved in human

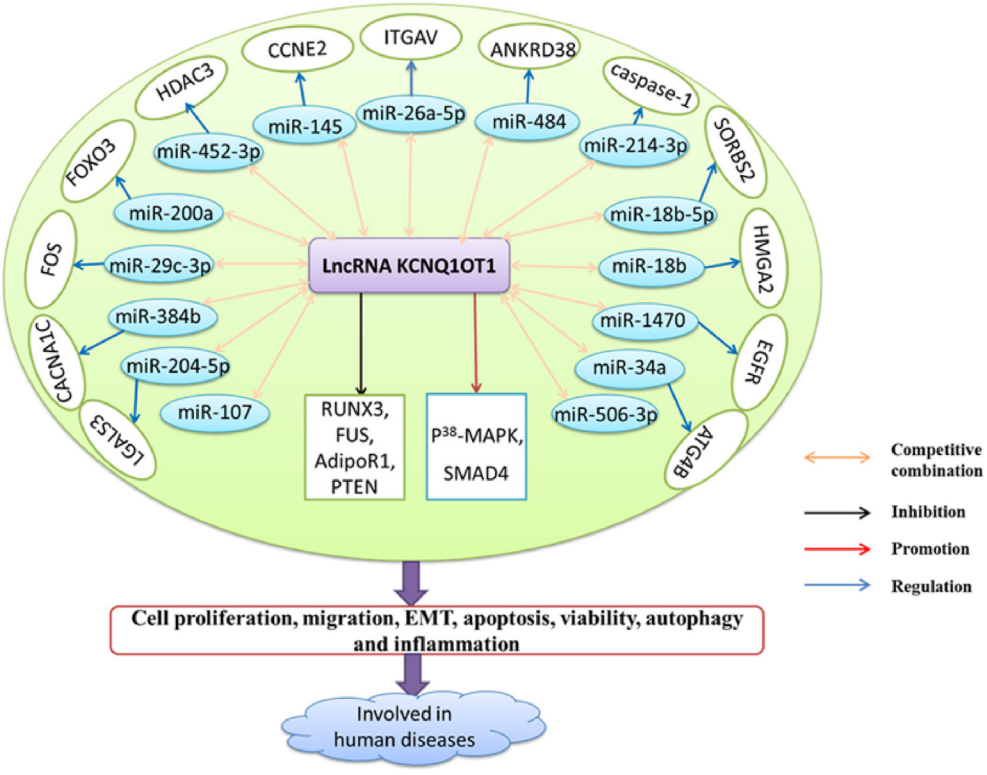

Figure 2 The mechanisms of KCNQ1OT1 affect cell function and regulating human diseases. EGFR, epidermal growth factor receptor; FOS, FBJ murine osteosarcoma viral oncogene homolog; FOXO3, forkhead box O3; FUS, fused in sarcoma; HMGA2, high mobility group protein A2; ITGAV, integrin αV; RUNX3, Runt-related transcription factor 3.

diseases. Most certainly, KCNQ1OT1 is expected to enter the clinic after solving some of the key issues in its clinical application.

Conflict of interests

The authors declare that they have no conflict of interest.

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Abbreviations

AF	atrial fibrillation
AMI	Acute Myocardial infarction
BMSCs	bone marrow mesenchymal stem cells
BWS	Beckwith-Wiedemann Syndrome
CAD	coronary artery disease
ceRNA	competitive endogenous RNA
CMEC	cardiac micro-vascular endothelial cell
CVD	cardio-cerebrovascular disease
DCM	diabetic cardiomyopathy
DN	diabetic nephropathy
DR	diabetic retinopathy
EGFR	epidermal growth factor receptor
EMT	epithelial-mesenchymal
FOXO3	forkhead box O3
FUS	fused in sarcoma
HF	heart failure
HMGA2	high mobility group protein A2
IR	ischemia reperfusion
lncRNA	long non-coding RNA
MI	myocardial infarction
ncRNA	non-coding RNA
OA	osteoarthritis
RUNX	Runt-related transcription factor
TNBC	triple-negative breast cancer

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