KCNQ1OT1

Subjects: Biology

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KCNQ1 Opposite Strand/Antisense Transcript 1 (KCNQ1OT1) encodes a lncRNA from the opposite strand of KCNQ1 in the CDKN1C/KCNQ1OT1 cluster that is reported to play a vital role in the development and progression of cancer.

KCNQ1OT1 human cancers long noncoding RNA

1. Basic Characteristics of Human Chromosome 11p15.5 and lncRNA KCNQ1OT1 Gene

KCNQ1 Opposite Strand/Antisense Transcript 1 (KCNQ1OT1), also known as KCNQ1 overlapping transcript 1, or LIT1, is a 91 kb un-spliced lncRNA located on chromosome 11p15.5 (**Figure 1**). The KCNQ1OT1 gene is part of a cluster of genes that undergo genomic imprinting, an epigenetic modification involving parent-specific gene expression modification. Genomic imprinting plays a critical role in fetal growth and development and is regulated by a nearby region of DNA known as imprinting center 2 (IC2) or KvDMR, which undergoes differential methylation [1][2]. The human CDKN1C/KCNQ1OT1 cluster exists as imprinted genes, expressing only one copy, with the allele activity depending on the parental origin. The paternally expressed KCNQ1OT1 transcript originates from intron 11 and is antisense to its associated protein-coding gene, Potassium Voltage-Gated Channel Subfamily Q Member 1 (KCNQ1) [3][4][5][6]. The antisense lncRNA KCNQ1OT1 promoter maps to KCNQ1 imprinting control regions, methylated on the maternal chromosome but un-methylated on the paternal chromosome.

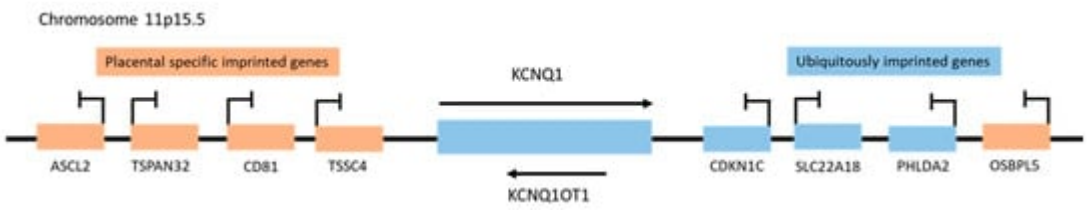

Figure 1. Schematic representation of imprinted gene clusters on human chromosome 11p15.5.

Genes located near the KCNQ1OT1 promoter (KCNQ1, CDKN1C, SLC22A18, and PHLDA2) that are imprinted both in the embryo and extra-embryonic tissues such as the placenta are ubiquitously imprinted genes, whereas the placental specific imprinted genes ASCL2, TSPAN32, CD81, TSSC4, and OSBPL5, and are only imprinted in the placenta (**Figure 1**) [7]. The ubiquitously expressed KCNQ1OT1 is more frequently localized in the nucleus, interacts with chromatin complexes, and regulates the genomic imprinting of multiple genes through bidirectional transcription-mediated silencing in cis [6][8][9]. Thus, the DNA sequences of the KCNQ1 and KCNQ1OT1 genes are

“read” in opposite directions and have very different functions. LncRNA KCNQ1OT1 is expressed in every tissue [10] and regulates genes vital for normal growth and development before birth, as well as postnatal behavior [6][11]. However, deletion of its promoter or early transcript termination results in a loss of KCNQ1OT1 and a disruption of imprinting in the CDKN1C/KCNQ1OT1 domain, which can lead to growth-related disorders (ex. Beckwith-Wiedemann syndrome) and cancer, as well as bi-allelic expression of the entire KCNQ1 domain [12].

2. KCNQ1OT1 in Human Cancers

In the present review, we will explore current knowledge on the role of KCNQ1OT1 in the development of various human cancers. We will thoroughly discuss the molecular and mechanistic role of KCNQ1OT1 in modulating oncogenic and biological functions, regulating cancer cell signaling mechanisms, and describe how its expression correlates to clinical features (**Table 1**). The interaction of KCNQ1OT1 and miRNAs or/and proteins and the potential targets in different cancers are summarized in **Figure 2**.

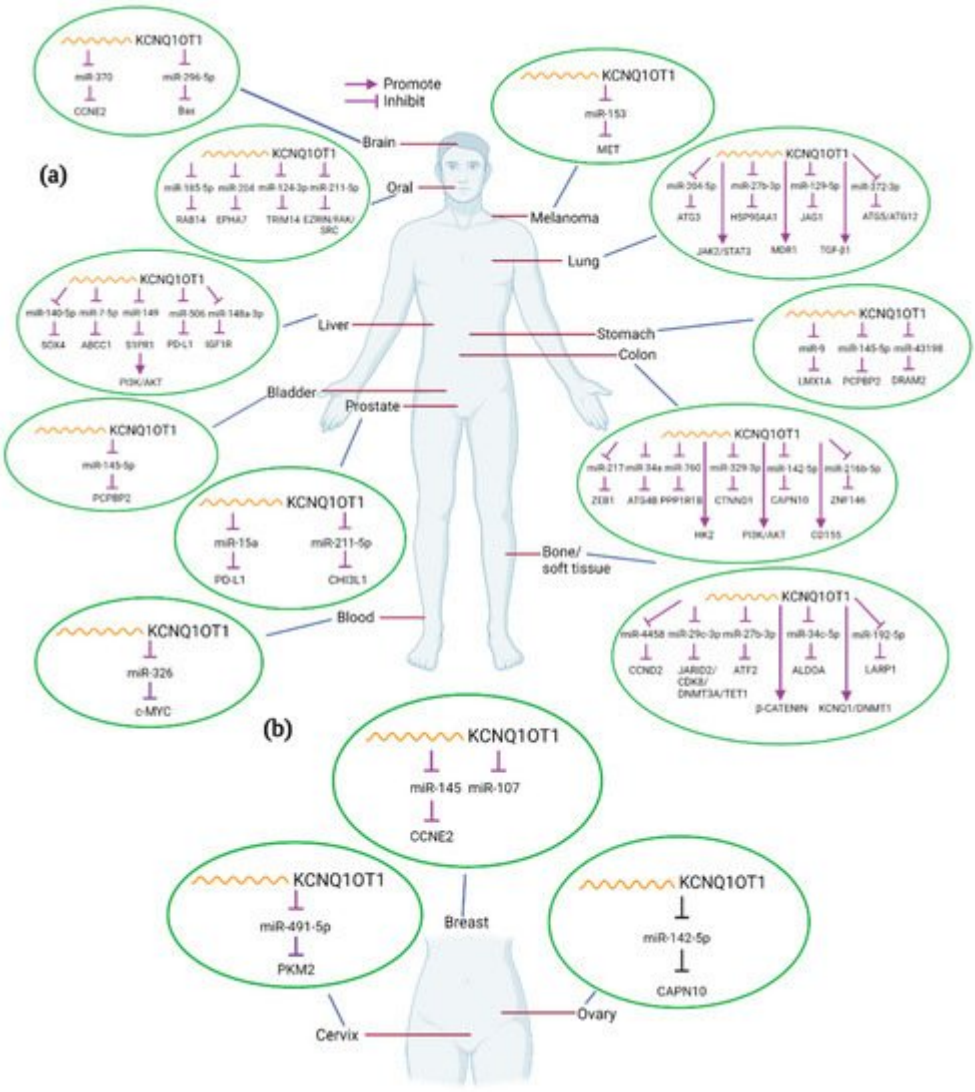

Figure 2. Interactions between KCNQ1OT1 and miRNA/genes in different kinds of human cancers. KCNQ1OT1 can interact with various miRNAs and genes in different tumor types (**a**), including female-specific cancers (**b**).

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Table 1. Functional characterization of lncRNA KCNQ1OT1 and its targets in various cancers.

Cancer	Expression Level	Role	Associated Clinical Features †	Functional Role †	Regulatory Molecule and Pathway [Reference]
Colorectal cancer	Upregulated	Oncogenic	Tumor size, TNM stage, lymph node metastasis, distant metastasis, histological differentiation, adjuvant therapy, primary tumor site, OS, DFS	Proliferation, cell cycle, apoptosis, migration, invasion, aerobic glycolysis, methotrexate resistance, adjuvant fluoropyrimidine-based chemotherapy	miR-217/ZEB1 [13]; miR-34a/Atg4B [14]; miR-760/PPP1R1B [3]; miR-329-3p/CTNND1 [15]; miR-216b-5p/ZNF146 [16]; HK2 [17]; PI3K/AKT [18]; CD155 [19]
Ovarian cancer	Upregulated	Oncogenic	OS	Proliferation, invasion,	miR-142-5p/CAPN10 [20]
Cervical cancer	Upregulated	Oncogenic	not investigated	Proliferation, metastasis, and radioresistance	miR-491-5p/PKM2 [21]
Glioma	Upregulated	Oncogenic	Histopathological grade	Proliferation, apoptosis, migration, invasion	miR-370/CCNE2 [22]
Neuroblastoma	not investigated	Suppressor	not investigated	Apoptosis	miR-296-5p/Bax [23]
Sarcoma	not investigated	not investigated	Histological type, metastasis, tumor depth, necrosis	not investigated	miR-29c-3p)/JARID2/CDK8/DNMT3A/TET1 [24]
Oral squamous cell carcinoma	Upregulated	Oncogenic	not investigated	Apoptosis, migration, invasion	miR-185-5p/Rab14 [25]
Tongue squamous cell carcinoma	Upregulated	Oncogenic	Clinical stage, node metastasis, survival status, cisplastin sensitivity	Proliferation, migration, invasion, cisplatin resistance	miR-211-5p/Ezrin/Fak/Src [26]; miR-124-3p/TRIM14 [7]
Maxillary sinus squamous cell	Upregulated	Oncogenic	not investigated	Viability, migration,	miR-204/EphA7 [27]

Cancer	Expression Level	Role	Associated Clinical Features †	Functional Role †	Regulatory Molecule and Pathway [Reference]
carcinoma				invasion,	
Acute myeloid leukemia	Upregulated	Oncogenic	not investigated	Proliferation, apoptosis, PMA-induced differentiation	miR-326/c-Myc [28]
Osteosarcoma	Upregulated	Oncogenic	not investigated	Proliferation, apoptosis, migration, invasion, EMT, aerobic gylcosis, fluorouracil resistance,	β-catenin [29]; KCNQ1/DNMT1 [30]; miR-4458/CCND2 [31]; miR-34c-5p/ALDOA [1]; miR-192-5p/LARP1 [2]
Chordoma	Upregulated	Oncogenic	not investigated	Multidrug resistance	miR-27b-3p/ATF2 [4]
Breast cancer	Upregulated	Oncogenic	Tumor size, tumor count, tumor stage	Proliferation, cell cycle, apoptosis, migration	miR-145/CCNE2 [5]; miR-107 [6]
Cholangiocarcinoma	Upregulated	Oncogenic	Tumor site, differentiation grade, tumor stage, TMN stage, lymph node metastasis, postoperative recurrence	Proliferation, apoptosis, invasion, EMT	miR-140-5p/SOX4 [8]
Hepatocellular carcinoma	Upregulated	Oncogenic	not investigated	Proliferation, viability, survival, apoptosis, migration, invasion, metastasis, oxaliplatin and sorafenib resistance	miR-7-5p/ABCC1 [9]; miR-149/S1PR1/PI3K/AKT [10]; miR-506/PD-L1 [11]; miR-148a-3p/IGF1R [12]
Bladder cancer	Upregulated	Oncogenic	Poor prognosis	Proliferation, apoptosis, migration, invasion	miR-145-5p/PCBP2 [32]
Lung cancer	Upregulated	Oncogenic	Tumor size, TNM stage, disease	Proliferation, cell cycle,	miR-204-5p/ATG3 [33]; MDR1 [34]; miR-27b-3p/HSP90AA1 [35]; miR-

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Cancer	Expression Level	Role	Associated Clinical Features †	Functional Role †	Regulatory Molecule and Pathway [Reference]
			stage, lymph node metastasis, histological differentiation, smoking history, OS	autophagy, apoptosis, migration, invasion, aerobic glycolysis, multidrug resistance, irradiation resistance	129-5p/JAG1 [36]; miR-372-3p/ATG5/ATG12 [37]; JAK2/STAT3 [38]; TGF-β1 [39]
Lung cancer	Upregulated	Suppressor	Clinical stage, tumor size, lymph node metastasis	Proliferation	not investigated [40]
Melanoma	Upregulated	Oncogenic	Poor prognosis	Proliferation, metastasis	miR-153/MET [41]
Prostate cancer	Upregulated	Oncogenic	not investigated	Proliferation, apoptosis, migration, invasion, metastasis	miR-15a/PD-L1 [42]; miR-211-5p/CHI3L1 [43]
Gastric cancer	Upregulated/Downregulated	Oncogenic/Suppressor	TNM stage, local invasion, lymph node metastasis, distant metastasis, histological grade	Proliferation, viability, survival, apoptosis, migration, invasion	miR-9/LMX1A [44]; miR-145-5p/ARF6 [45]; miR-43198/DRAM2 [46]

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Key: †, TNM, (tumor lymph node metastasis), overall survival (OS), disease-free survival (DFS), epithelial–mesenchymal transition (EMT).

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3. Regulatory Mechanisms of KCNQ1OT1

3.1. Impact of KCNQ1OT1 on microRNA Regulation

LncRNAs acting as ceRNAs with miRNAs are the most frequently identified biological function of lncRNAs and has been associated with various cancers, such as liver [33][47], prostate [48], ovarian [20][49], colorectal [50], and glioblastoma multiforme [51]. By sponging miR-217, KCNQ1OT1 upregulated zinc finger E-box binding homeobox 1 (ZEB1) and regulated CRC cell proliferation, migration, and EMT formation [13] (**Table 1**). Similarly, the miR-329-3p/CTNND1 (Catenin delta-1) axis was demonstrated to interact with KCNQ1OT1 to modulate SW480 and LS1034

CRC cell proliferation, migration, and invasion, and apoptosis [15]. In a xenograft mouse model, knockdown of KCNQ1OT1 inhibited CRC cell growth and decreased tumor volume, while overexpression of KCNQ1OT1 induced protective autophagy and chemoresistance to oxaliplatin (OXA) by sponging miR-34a and upregulating autophagy-related 4B (Atg4B) [14]. Sun et al., showed that KCNQ1OT1 acted as a sponge of miR-204 in the progression of MSSCC and explored the role of ceRNA regulation of the KCNQ1OT1/miR-204/EphA7 axis [27]. Cell-based studies indicate that KCNQ1OT1 knockdown inhibited cell proliferation and promoted apoptosis and cell differentiation in HL-60 and U937 AML cells by acting as a ceRNA for miR-326 and targeting c-Myc (myc proto-oncogene, basic helix-loop-helix (bHLH) transcription factor) [28]. Loss of KCNQ1OT1 inhibited BRCA cell proliferation and migration in BT-549 and HCC1599 cells and reduced tumor growth in vivo by sponging miR-107 [6] (**Table 1**). Additional experiments are needed to investigate whether cyclin-dependent kinase 8 (CDK8) is involved in the epigenetic regulation of the KCNQ1OT1–hsa-miR-107 axis, as CDK8 has been previously shown by Li et al. to regulate miR-107 in BRCA [52].

KCNQ1OT1 serves as ceRNA to regulate multidrug resistance via regulating miR-27b-3p/activating transcription factor 2 (ATF2) in human chordoma bone tumor cells [4]. Zhu et al. hypothesized that KCNQ1OT1 is correlated with poor prognosis in patients with soft tissue sarcoma (STS), competitively binds with miR-29c-3p, regulating JARID2, CDK6, DNMT3A, and TET [24] (**Table 1**). Thus, this intricate ceRNA network may serve as a therapeutic target for treating the STS sub-cluster of patients with a poor prognosis. KCNQ1OT1 upregulation induced cell proliferation and migration and inhibited apoptosis in HOS and U2OS OS cells through competitive binding of miR-4458 and upregulating cyclin D2 (CCND2) [31]. KCNQ1OT1 also promoted U2OS and 143B OS cell proliferation by enhancing aerobic glycolysis through competitive binding to miR-34c-5p and stimulating aldolase A (ALDOA) expression in vitro and in vivo [1] (**Table 1**).

KCNQ1OT1 acts as a competing endogeneous RNA (ceRNA) for miR-145-5p, resulting in increased expression of poly(rC) binding protein 2 (PCBP2). PCBP2 is a target of miR-145-5p, and its overexpression results in the progression of BC by modulating cell proliferation, migration and invasion, and cell apoptosis [32] (**Table 1**). Therefore, KCNQ1OT1 expression may identify the subset of BC patients with a more aggressive phenotype. Wang et al., have shown that KCNQ1OT1 also sponged miR-129-5p and regulated Jagged canonical Notch ligand 1 (JAG1) expression that induces proliferation, migration, and invasion of A549 and H460 NSCLC cells [36] (**Table 1**). KCNQ1OT1 was upregulated in radiation-resistant LAD cells and is associated with the low response to anticancer treatment and poor prognosis of LAD patients [37]. Knockdown of KCNQ1OT1 increased radiosensitivity both in vitro and in vivo by sponging miR-372-3p and regulating autophagy-related targets (ATG5 and ATG12), thereby inhibiting autophagy (**Table 1**). KCNQ1OT1 is aberrantly upregulated in melanoma and retinoblastoma (RB) patient tissues compared with adjacent normal tissues [41][53][54]. Overexpression of KCNQ1OT1 contributed to the proliferation, migration, and invasion of melanoma and RB cells by sponging miR-185, and increasing MET proto-oncogene receptor tyrosine kinase (MET) and hypoxia-inducible factor-1α (HIF-1α) expression, respectively [41][53] (**Table 1**). KCNQ1OT1 also acts as a ceRNA for miR-124 to promote RB cell progression by regulating the transcription factor, specificity protein 1 (SP1) expression, and the silent information regulator 1 (SIRT1)/c-Jun N-terminal kinase (JNK) signaling pathway [54].

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3.2. Impact of KCNQ1OT1 on Cell Signaling Pathways

An increasing number of studies have demonstrated that lncRNAs modulate oncogenic signaling [55][56], highlighting their utility as diagnostic markers and therapeutic targets [25]. Several studies have revealed that KCNQ1OT1 is overexpressed in SCLC patients and is associated with a poor prognosis. Downregulation of KCNQ1OT1 inhibits SCLC cell proliferation, migration, and invasion, induces apoptosis, and suppresses tumor growth and chemoresistance via TGF-β-mediated EMT signaling [49] and the Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) signaling pathway [48]. Duan et al. reported that KCNQ1OT1 promoted the malignancy SW620 and RKO CRC cells by upregulation of the PI3K/AKT signaling pathway [34]. Moreover, KCNQ1OT1 promoted LC cell proliferation, migration, invasion, and EMT in cisplatin-resistant cells by activating β-catenin [57].

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