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Crosstalk mechanisms between the WNT signaling pathway and long non-coding RNAs

Vasiliki Zarkou [a, b], Alexandros Galaras [a, c], Antonis Giakountis [a, d], Pantelis Hatzis [a, *]

[a] Biomedical Sciences Research Center 'Alexander Fleming', 16672 Vari, Greece
[b] School of Biology, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece
[c] Department of Medicine, National and Kapodistrian University of Athens, 11527 Goudi, Greece
[d] Department of Biochemistry and Biotechnology, University of Thessaly, 41500 Larissa, Greece

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ABSTRACT

The WNT/β-catenin signaling pathway controls a plethora of biological processes throughout animal development and adult life. Because of its fundamental role during animal lifespan, the WNT pathway is subject to strict positive and negative multi-layered regulation, while its aberrant activity causes a wide range of pathologies, including cancer. At present, despite the inroads into the molecules involved in WNT-mediated transcriptional responses, the fine-tuning of WNT pathway activity and the totality of its target genes have not been fully elucidated. Over the past few years, long non-coding RNAs (lncRNAs), RNA transcripts longer that 200nt that do not code for proteins, have emerged as significant transcriptional regulators. Recent studies show that lncRNAs can modulate WNT pathway outcome by affecting gene expression through diversified mechanisms, from the transcriptional to post-translational level. In this review, we selectively discuss those lncRNA-mediated mechanisms we believe the most important to WNT pathway modulation.

1. Introduction

The WNT signaling cascade is highly conserved among species and controls a multitude of biological processes during animal development and life-cycles. Because of its central role in the maintenance of tissue homeostasis, the WNT pathway is tightly regulated at multiple levels, from the ligand-receptor interaction down to transcriptional and post-transcriptional levels; its aberrant activity has been implicated in a number of developmental disorders and diseases and, most prominently, in cancer [1]. Although the main molecular players of this pathway have been well characterized, aspects of its function, including the fine-tuning of its activity and the totality of its target genes remain incompletely understood. The recent discovery of long non-coding RNAs (lncRNAs) that are regulated by WNT and/or participate in WNT pathway modulation and outcome is particularly intriguing and has highlighted some of these gaps in our knowledge [2,3].

LncRNAs comprise a group of non-coding transcripts, arbitrarily defined as being longer than 200nt, that are transcribed from the human and other genomes but do not code for proteins [4,5]. Despite the lack of obvious protein-coding potential, functionality has been assigned to several lncRNAs. They have been shown to participate in many cellular processes such as gene imprinting [6], differentiation and development [7], antiviral immunity [8] and transcriptional responses [9,10]. Therefore, deregulation of lncRNA expression and function is implicated in the pathogenesis of several diseases, including cancer [2,11], metabolic [12,13], cardiovascular [14], neurodegenerative [15] and inflammatory pathologies [16,17].

In this review, we summarize our knowledge on the WNT signaling cascade both in normal and disease conditions. In addition, we provide a brief overview of the progress made in the lncRNA field, focusing mainly on lncRNA activities in modulating gene expression. Finally, we highlight the molecular mechanisms underlying the crosstalk between WNT/β-catenin signaling and lncRNAs, as well as the relevance of this interplay in different pathological conditions.

2. WNT/β-catenin signaling pathway

The WNT signaling cascade is divided into β-catenin dependent

* Corresponding author.
E-mail address: hatzis@fleming.gr (P. Hatzis).

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(WNT/β-catenin) [1] and β-catenin-independent signaling branches (WNT/Planar Cell Polarity, WNT/Calcium and WNT/JNK pathways) [18]. The WNT/β-catenin signaling pathway, also known as the canonical WNT pathway, is better characterized and comprises signal transduction from the extracellular membrane to the nucleus through the accumulation of β-catenin protein [1]. In unstimulated cells, the cytoplasmic levels of β-catenin are maintained low by a destruction complex consisting of tumor suppressor proteins adenomatous polyposis coli (APC) and Axin2 and the kinases casein kinase1 (CK1) and glycogen synthase kinase 3β (GSK3β) [1]. The constitutively active CK1 and GSK3β kinases phosphorylate Axin-bound β-catenin at a series of Ser/Thr conserved residues [19] inducing the recruitment of the F-box-containing protein E3 ubiquitin ligase β-TrCP [20]. The subsequent ubiquitination of phospho-β-catenin triggers its proteasomal degradation [21] thereby abrogating its nuclear translocation. In the absence of nuclear β-catenin, its effector T cell Factor (TCF)/Lymphoid Enhancer Factor (LEF) transcription factors [22,23] interact with Groucho proteins, mediating transcriptional repression of WNT target genes [24,25]. Binding of WNT ligands to their cognate Frizzled (Fzd) receptors induces the formation of a heterodimeric complex consisting of Fzd and low density lipoprotein receptor-related protein 5/6 (LRP5/6) co-receptors [26,27]. This leads to a conformational change of the cytoplasmic tail of LRP5/6, making it accessible to phosphorylation by several protein kinases. As a result, the Axin2 protein is recruited to the cell membrane by interacting both with the phospho-tail of LRP5/6 and the Dishevelled (Dsh) protein, which binds to the cytoplasmic part of Fzd receptors, leading to inactivation of the destruction complex and stabilization of β-catenin [1,28,29]. Accumulated cytoplasmic β-catenin then migrates to the nucleus, where it engages context-dependent DNA-bound TCF/LEF transcription factors, converting them to transcriptional activators [1,29]. Aberrant WNT/β-catenin activation, due to mutations in components of the destruction complex or β-catenin itself, is a common hallmark of many cancers, resulting in the expression of WNT target genes with oncogenic functions [30].

WNT proteins are not the only ligands of Fzd/LRP receptors; there are several molecules competing with WNTs for binding. WNT antagonists of the Dickkopf (DKK) and the Sclerostin/SOST families block the WNT signaling cascade by binding to LRP5/6 and abrogating its subsequent dimerization with Fzd [31,32]. Similarly, secreted Frizzled-related proteins (sFRPs) bind and inactivate Fzd receptors. Other WNT inhibitors function by binding to and neutralizing WNTs. For example, WNT inhibitory proteins (WIF) bind WNTs, thereby preventing pathway activation [26]. Similarly, APCDD1, a membrane-bound glycoprotein, disrupts WNT signaling by binding both WNT ligands and LRP [33]. On the other hand, Norrin (NDP) and R-spondins (RSPO) function as WNT agonists by binding and activating Fzd receptors [1]. The Norrin protein interacts specifically with the Fzd-4/LRP5 complex and activates signal transmission into cells during retinal vascularization, while R-spondin 1-4 proteins interact with Lgr4/5/6 receptors and enhance signaling at low WNT levels [34–37]. Binding of R-spondins to Lgr4/5/6 receptors enhances WNT signaling by clearing the cell-surface transmembrane E3 ubiquitin ligases, zinc and ring finger 3 (ZNRF3) and its homologue, ring finger 43 (RNF43), from the plasma membrane. RNF43 and ZNRF3 ligases ubiquitinate the cytoplasmic tails of Fzd receptors, inducing their rapid endocytosis and lysosomal degradation, inhibiting the WNT pathway [37–39].

2.1. WNT/β-catenin signaling function and dysfunction

The WNT/β-catenin signaling cascade plays crucial roles in animal life by controlling various genetic programs during embryonic development and adult homeostasis [40]. Specifically, WNT, along with other signaling pathways, such as TGF-β, Hedgehog, Notch and Receptor Tyrosine kinases, participate in controlling cellular proliferation, differentiation, cell migration and apoptosis [40]. It is therefore not surprising that aberrant function of these pathways leads to severe developmental perturbations and lethality [40]. The same pathways also play significant roles in the maintenance of tissue homeostasis and regulate stem cell functions during adult life [40]. Stem cells possess the ability to self-renew, while also giving rise to the specialized cells maintaining tissue architecture and homeostasis [41]. The WNT/β-catenin pathway has been found to be required for the maintenance of many stem-cell types by controlling, among others, the expression of LGR5 and AXIN2, two stem cell specific genes [42,43]. Both Lgr5 and Axin2 have been used in lineage tracing experiments, increasing our knowledge about WNT-regulated adult stem cells in many organs and tissues [44–48]. A representative example for the dependence of stem-cell self-renewal on WNT/β-catenin signaling is the mammalian intestinal epithelium; genetic ablation of Tcf4 in mice results in epithelial breakdown due to the loss of intestinal stem cells [49]. In other examples, inhibition of WNT signaling by overexpression of DKK (WNT antagonist) eliminates hair follicles and disrupts the mammary gland by influencing the residing stem cells and their progenitors [44,50,51]. Similarly, in the hematopoietic system, overexpression of Axin (a negative regulator of the WNT pathway) decreases the number of transplantable stem cells [52]. On the other hand, activation of WNT signaling in the presence of WNT ligands or by using constitutively active forms of β-catenin leads to stem cell expansion in hematopoietic and hair follicle systems, respectively [53,54].

Given the importance of the WNT/β-catenin signaling cascade for adult stem cell biology, it is expected that mutations in its components are frequently observed in cancer, mainly in tissues that normally depend on WNT for self-renewal and repair [55]. One of the most well-established examples is colon cancer. Familiar adenomatous polyposis (FAP) is a hereditary cancer syndrome caused by germline mutations in the APC gene [56–58]. FAP patients carry heterozygous APC mutations, and loss of heterozygosity leads to the formation of polyps in adulthood. Additional mutations in oncogenes or tumor suppressor genes drive these polyps towards malignancy. In sporadic colorectal cancers, both APC alleles are frequently lost, resulting in β-catenin stabilization and constitutively activated WNT signaling that fuels cancer cell growth [59]. Inactivating mutations in other WNT pathway components such as Axin2 [60], β-catenin [61], RNF43 [62] and ZNRF3 [63] have also been reported to cause a variety of carcinomas in different tissues.

3. LncRNAs in the WNT signaling cascade

In recent years, lncRNAs have gained prominence as integral regulators of gene expression from the transcriptional to the post-transcriptional and translational levels; they have also been shown to respond to signaling molecules and to affect signal-dependent cell functions [64]. LncRNAs crosstalk with a variety of key signaling networks, such as WNT [65,66], Notch [67], TGFβ [68,69] and p53 [64], and affect many cellular pathways and biological processes, including oncogenic signaling. Recent advances in biomedical research have allowed the implementation of experimental and bioinformatic approaches to identify WNT-associated lncRNAs as both regulators and targets of the WNT/β-catenin signaling cascade.

3.1. The emergence of long non-coding RNAs

In 2007, the Encyclopedia of DNA elements (ENCODE) project, an

international consortium involved in building a comprehensive list of functional elements in the human genome, revealed that the vast majority (60–80%) of the human genome is transcribed, while only ~1.5% of the genome encodes protein-coding genes [70]. The observed discrepancy prominently raised the question of the nature of this non-coding transcription, revealing the functional importance of non-coding transcripts (miRNAs, lncRNAs, etc). The newly discovered lncRNAs can be further categorized as intronic, antisense or intergenic, depending on their location and/or as nuclear, nucleolar or cytoplasmic depending on the cellular compartment they are located in [71]. Most of the annotated lncRNAs are transcribed by RNA polymerase II and are 5′-prime capped, polyadenylated and alternatively spliced, just like mRNAs. Moreover, these loci show all the hallmarks of bonafide active genes, including conserved promoters decorated with histone H3 lysine 4 trimethylation (H3K4me3), histone H3 lysine 36 trimethylation (H3K36me3) over the gene bodies and regulation by conventional morphogens and transcription factors [72–74]. However, lncRNAs show lower evolutionary conservation and they are expressed at lower levels, but in a more tissue-specific manner, compared to mRNAs [75,76].

3.2. Long non-coding RNA functions

Because lncRNAs do not encode proteins, research into their functions has so far relied mainly on loss-and gain-of function studies. Knock-down of lncRNAs expression is feasible, using chemically engineered antisense oligonucleotides (ASOs), si- or sh-RNA-based techniques and, more recently, Cas9-mediated genome engineering approaches [77–79]. Changes in lncRNA expression are frequently associated with phenotypic alterations in cultured cells or animal models, giving information about their function [79]. Depending on their subcellular distribution, lncRNAs exert their functions through different mechanisms. Nuclear lncRNAs affect gene expression by interacting with chromatin-modifying complexes, participating in higher-order chromatin organization or modulating the activity of transcriptional enhancers [9,10,80,81]. Other nuclear acting lncRNAs interfere with the transcriptional machinery or participate in the formation of subnuclear structures, such as nuclear speckles and paraspeckles [82–84]. Cytoplasmic lncRNAs frequently function as splicing or translational regulators or as miRNA decoys, titrating the latter away from their target mRNAs [85]. In addition, they interact with proteins and modulate their stability [86,87].

3.3. LncRNAs and transcriptional regulation

LncRNAs may regulate transcription by acting locally, at or around the sites of their own genic locus, or distally, at sites that are located on other chromosomes, by recruiting regulatory protein complexes (e.g. chromatin modifiers, chromatin organizers and/or transcription factors) [88–90]. Once they are transcribed, lncRNAs can accumulate at their sites of synthesis and act *in cis*, regulating the expression of their neighboring genes. For example, lncRNA CCAT1-L is transcribed from the upstream super-enhancer region of the MYC gene and increases MYC expression by interacting with the chromatin organizer CTCF, promoting chromosome looping [91]. Else, they can accumulate at their site of transcription but act *in trans*, regulating genes located far away in the same or in different chromosomes by affecting chromatin organization [88]. FiRRE is an example of a *trans*-acting lncRNA that is transcribed from the X chromosome and, by promoting 3D chromatin organization, participates in long-range chromatin interactions [92].

A second paradigm of nuclear lncRNA function involves translocation from the site of synthesis in order to regulate gene expression either globally or in a gene-specific manner [88]. To this effect, lncRNAs base-pair with other RNAs, bind directly to DNA or participate in RNA-protein interactions [82]. HOTAIR is one of the best-characterized lncRNAs belonging in this group. During developmental patterning of cells into tissues and organs, HOTAIR is transcribed from the HOXC locus and interacts with the PRC2 histone modification complex to suppress the expression of the HOXD locus [93,94]. Moreover, it participates in the formation of RNA:DNA:DNA triplexes with many other genomic sites, through its GA-rich motif, recruiting chromatin modifiers and affecting gene expression globally [95]. LncRNAs that participate in the formation of specific nuclear bodies also belong in the group of *trans*-acting non-coding transcripts [88]. These membrane-less structures contain many regulatory proteins and lncRNAs that contribute to specific nuclear processes. For example, MALAT1 localizes in nuclear speckles, where it modulates the levels of active Ser/Thr splicing factors affecting alternative splicing of many genes [96]. Moreover, the NEAT1 lncRNA is indispensable for the integrity of paraspeckles and is implicated in mRNA nuclear retention [83].

LncRNAs may also regulate transcription indirectly, through the act of transcription itself [88]. In these cases, transcription of a specific lncRNA locus may affect positively (by maintaining open chromatin) or negatively (by sequestering away RNA pol II and regulatory proteins) the transcription of its neighboring genes [88]. The transcript itself may have no activity at all or participate in a different function. For example, the transcription of the Airn gene leads to silencing of the overlapping Igf2R gene in mice while the transcript itself does not possess any function [97]. Similarly, abolishment of the transcription of lncRNA upperhand (Uph) disrupts the expression of its downstream developmental gene Hand2 in the heart, whereas loss of the mature Uph transcript itself has no effect [98].

4. Crosstalk mechanisms of WNT/β-catenin signaling and lncRNAs

The signaling molecules that participate in the WNT pathway and the WNT-regulated genes can ultimately impact gene expression by functioning as transcription factors themselves and/or regulating the activity of many transcription and epigenetic factors and chromatin organizers either directly or indirectly. Emerging evidence suggest that lncRNAs are involved in WNT pathway outcome by regulating gene expression through different mechanisms from the transcriptional to post-translational level [65,66]. In this review, we selectively discuss those lncRNA-mediated mechanisms we believe the most important to WNT pathway modulation (summarized in Table 1).

4.1. LncRNAs interacting with transcriptional regulators

Many of the proteins that participate in eukaryotic transcription, apart from DNA also bind lncRNAs in vitro and in vivo. These proteins either have separate DNA and RNA binding sites or the two nucleic acids bind mutually exclusively in overlapping binding regions, pointing in both cases to an RNA-driven regulatory role [82].

The human 8q24 gene desert, located upstream of MYC gene, contains multiple regulatory elements; one of these encompasses the SNP rs6983267, which maps to a functional TCF4 binding site in CRC cells and affects the binding of the WNT-regulated transcription factor TCF4 and the subsequent recruitment of β-catenin [99,100]. The same region has been shown to express distinct WNT-regulated lncRNAs in different human tumors including CCAT1-L, CCAT1-S, CCAT2 and CASC11 [66]. CCAT2 (colon cancer associated transcript 2) is a lncRNA of ~400nt that is transcribed in the sense orientation from the highly conserved 8q24 chromosomal region

Table 1
Summary of lncRNAs that are regulated by or modulate WNT signaling pathway.

Name	Role in cancer	Crosstalk with WNT/β-catenin signaling	Mechanism of function	Type of cancer	References
CCAT-2	Oncogene	WNT-activated Activates the expression of c-Myc gene	Transcriptional activation of WNT target genes by interacting with the TCF4 transcription factor and participating in chromatin looping	Colorectal Cancer	[99–101]
ASBEL	Oncogene	WNT-activated Activates the expression of WNT target genes	Transcriptional repression of ATF3 protein by interacting with TCF3	Colorectal Cancer (plus undefined WNT-mediated role in ovarian cancer)	[3]
RBM5-AS1	Oncogene	Activation of WNT pathway	Transcriptional activation of WNT target genes by interacting with β-catenin	Colorectal Cancer	[105]
CCAL	Oncogene	Activation of WNT pathway	Targets for degradation the AP-2a protein, a negative regulator of WNT pathway	Colorectal Cancer (plus undefined WNT-mediated role in osteosarcomas)	[107]
mrhl	Tumor Suppressor	WNT-suppressed Inhibition of WNT pathway	Interacts with Ddx5/p68 and destabilizes β-catenin	No demonstrated role in cancer (Differentiation of spermatogonia to spermatocytes)	[111,113,114]
LincRoR	Oncogene	Activation of WNT pathway	Interacts with the hnRNP-I and AUF1 and stabilizes MYC mRNA	Colorectal Cancer (plus undefined WNT-mediated role in breast and ovarian cancers)	[116,117]
CASC11	Oncogene	WNT-activated Activates the expression of WNT target genes	Interacts with the hnRNP-K and promotes β-catenin nuclear accumulation	Colorectal Cancer	[119,120]
MYU	Oncogene	WNT-activated Activates the expression of WNT target genes	Interacts with the hnRNP-K and stabilizes CDK6 mRNA	Colorectal Cancer	[11]
Lnc34a	Oncogene	Activation of WNT pathway	Interacts with DNMT3a/PHB2 and HDAC1 epigenetic regulators to suppress miR-34a expression	Colorectal and Prostate Cancer	[85,122]
NBAT1	Tumor suppressor	Inhibition of WNT pathway	Interacts with the EZH2 subunit of the PRC2 complex and inhibits H3K27me3 on the DKK1 promoter	Breast Cancer	[123]
H19	Both Oncogene and tumor suppressor	Activates or inhibits WNT pathway	Interacts with the EZH2 subunit of the PRC2 complex and enhances H3K27me3 on the Nkdl promoter Interacts with the macroH2A protein and increases the expression levels of CDK8 which regulates β-catenin activity	Bladder and Colorectal cancer	[132,133]
WiNTRLINC1	Oncogene	WNT-activated Activates the expression of ASCL2 gene	Transcriptional activation of ASCL2 by promoting chromatin looping	Colorectal Cancer	[2]
HNF1A-AS1	Oncogene	Activation of WNT pathway	Competing endogenous RNA for miR34a	Colorectal Cancer	[138]
PTCSC3	Tumor suppressor	Inhibition of WNT pathway	Competing endogenous RNA for miR-574-5p	Thyroid Cancer	[143,146]
uc.158	Oncogene	WNT-activated Activates WNT pathway	Competing endogenous RNA for miR-193b	Hepatocellular Carcinoma	[147]
CCAT1-S	Oncogene	WNT-activated Activates WNT pathway	Competing endogenous RNA for let-7 Interacts with the EZH2 subunit of the PRC2 complex and enhances H3K27me3 on the promoter of miR-200b	Colorectal and Lung Cancer, Hepatocellular Carcinoma	[151–154]

next to the MYC gene and encompasses the rs6983267 SNP [101]. CCAT2 has been shown to physically interact with the TCF4 (TCF7L2) transcription factor, increasing its transcriptional activity in CRC [101]. The subsequent activation of the WNT/β-catenin-mediated transcriptional program results in increased expression of genes involved in genomic instability and cell proliferation and promotes cancer growth [101]. Specifically, CCAT2/TCF4-driven activation of MYC increases the expression of its downstream target genes, such as miR-17-5p and miR-20a, resulting in increased cell invasion and metastasis [101]. TCF4 also regulates the expression of the CCAT2 transcript itself by binding to the consensus TCF4 element located within rs6983267, implying the existence of a positive regulatory feedback loop that further explains the SNP-conferred CRC risk [100,101]. In a recent study, CCAT2 was also found to reprogram the metabolism of cancer cells by interacting with the Cleavage Factor I (CFIm) complex and fine-tuning the alternative splicing of glutaminase (GLS) [102]. As described for CCAT2, aberrant glutamine metabolism has also been associated with genomic instability and cancer propagation [101,103].

Similarly, the lncRNA ASBEL [antisense ncRNA in the abundant in neuroepithelium area (ANA/B-cell translocation gene 3 (BTG3) locus] is another WNT-regulated lncRNA that modulates WNT pathway outcome by interacting with the TCF3 transcription factor [3]. ASBEL was firstly identified as an antisense transcript of the ANA/BTG3 gene required for proliferation and tumorigenicity of ovarian cancer cells [104]. However, in contrast to ovarian and breast cancers, loss of ANA/BTG protein does not restore the viability defect of colon cancer cells in which ASBEL is also knocked down, suggesting that ASBEL mediates its proliferative effects in an ANA/BTG independent manner. In these cells ASBEL was found to be transcriptionally activated by β-catenin and to interact with the TCF3 transcription factor, promoting WNT/β-catenin mediated cell proliferation [3]. Moreover, ASBEL/TCF3 complex formation recruits TCF3 on the transcription start site of the ATF3 gene, a known tumor suppressor that inhibits tumor growth and metastasis in many cancer types, repressing its expression and increasing the

tumorigenicity of colon cancer cells. Furthermore, ATF3 was identified as a negative regulator of ASBEL expression, as well as of other β-catenin target genes, completing a negative feedback loop in intestinal cells [3].

Another lncRNA, RBM5-AS1 (RBM5 antisense 1) or LUST (Luca-15 specific transcript) was also found to function as a transcriptional regulator of the WNT pathway [105]. RBM5-AS1 is highly expressed during sphere formation of colon cancer initiating cells but its expression is significantly lower in differentiated spheres with more adherent morphology. Loss of RBM5-AS1 expression decreases the levels of known WNT target genes such as AXIN2, CCND1 and TCF4 and reduces the levels of active β-catenin, while its overexpression enhances WNT/β-catenin signaling. Moreover, high levels of RBM5-AS1 activate the expression of stemness markers, such as CD24 and CD44, conferring a stem-cell like phenotype in tumor initiating cells [105]. Mechanistic analyses showed that RBM5-AS1 is mostly localized in the nucleus, where it binds β-catenin and facilitates its interaction with the TCF4 transcription factor (Fig. 1) [105,106]. As a result, the occupancy of β-catenin/TCF4 complexes on β-catenin target promoters is increased, amplifying WNT signaling and maintaining the self-renewal of colon cancer initiating cells [105].

LncRNA profile analysis in intestinal cells revealed that the expression of another lncRNA named CCAL (colorectal cancer-associated lncRNA) is increased during the progression from normal colorectal tissues to adenoma and carcinoma and is correlated with poor prognosis [107]. Histone modification analysis in intestinal cancer cells revealed decreased histone H3 methylation and increased histone H3 acetylation on the CCAL promoter region, resulting in high CCAL levels in CRC. CCAL was found to interact with the AP-2α protein, promoting its ubiquitination and proteasomal degradation (Fig. 1). Because AP-2α is a negative regulator of the WNT/β-catenin pathway, CCAL regulates CRC progression by activating indirectly the WNT signaling cascade. Moreover, CCAL-mediated activation of the WNT pathway increases the expression of the MDR1/P-gp gene, which has been associated with multidrug resistance in colorectal cancer, explaining the negative clinical association between CCAL levels and adjuvant chemotherapy outcome in colon cancer patients [107]. Recently, CCAL was also associated with metastatic osteosarcomas, but its mode of function in this type of cancer is still under investigation [108].

Mammalian spermatogenesis is a WNT-regulated developmental process, encompassing a mitotic, a meiotic and a spermiogenesis phase [109]. During these phases, the generated spermatogonial cells give rise to genetically diverse haploid spermatids, which mature to sperm through nuclear reshaping and chromatic packaging. WNT signaling controls the meiotic commitment and differentiation of B type spermatogonia to meiotic spermatocytes and is negatively regulated by the mrhl (meiotic recombination hot spot locus) RNA during this process [110,111]. Mrhl is expressed during the mitotic phase of spermatogenesis and localizes to the nucleus of mouse spermatogonial cells, where it interacts, among others, with the Ddx5/p68 protein, keeping it in a dephosphorylated state and retaining it in the nucleus [111]. In synergy with Ddx5/p68, mrhl occupies several genomic loci and directly regulates the expression of WNT target and spermatogenesis specific genes [112]. However, during the meiotic progression of spermatogenesis, elevated WNT3a levels activate the WNT/β-catenin signaling cascade and down-regulate the expression of mrhl [113]. The mechanism of mrhl down-regulation is executed mainly through a putative TCF4 binding site in its proximal promoter region. Binding of TCF4/β-catenin complex on the mrhl promoter recruits the co-repressor Ctbp1 and Ctbp1-associated proteins (such as p300, G9a, Hdac1 and Hdac2) resulting in the deposition of repressive histone marks at the mrhl promoter and decreased mrhl expression [113]. Upon mrhl down-regulation, the Ddx5/p68 protein remains free and translocates into the cytoplasm where it is tyrosine-phosphorylated. In this phosphorylated form, Ddx5/p68 stabilizes β-catenin and triggers its nuclear translocation resulting in increased TCF4/β-catenin-mediated transcriptional activity [111]. As a result, WNT-mediated down-regulation of mrhl activates the expression of various pre-meiotic and meiotic marker genes, such as Sox8, to facilitate the differentiation of spermatogonia to spermatocytes [114].

4.2. *LncRNAs participating in ribonucleoprotein complexes*

As master regulators of gene expression, lncRNAs can form lncRNA–protein (ribonucleoprotein) complexes to regulate a large number of genes. These complexes function either at the post-transcriptional or translational level to regulate the expression of their targets [88]. Linc-RoR (lincRNA regulator of reprogramming) was firstly identified as a regulator of reprogramming in iPSCs, but was later also implicated in many types of cancer, including oral, colorectal, ovarian, and breast cancers [115–118]. In colon cancers, high levels of linc-RoR promote cell proliferation and tumor growth due to upregulation of MYC [116]. Linc-ROR

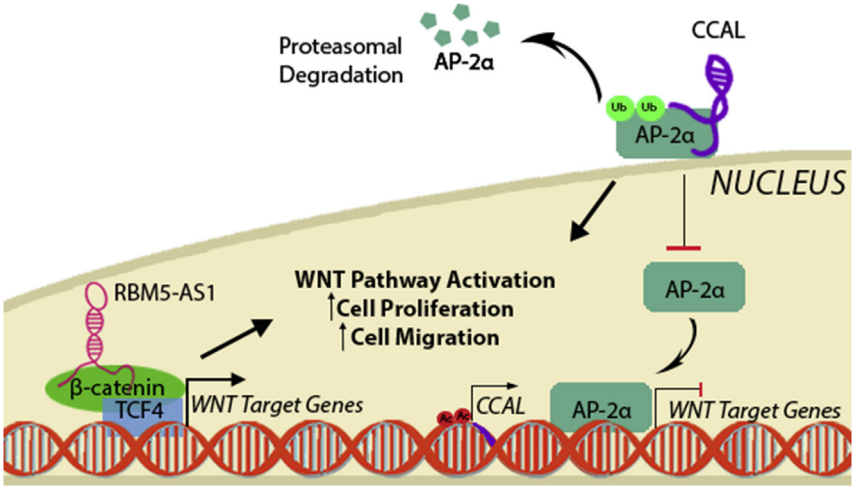

Fig. 1. Several lncRNAs interact with transcription factors recruiting them to their target genes (e.g. RBM5-AS1) while others titrate them away from their DNA targets (e.g. CCAL).

regulates the expression of MYC post-transcriptionally by affecting its mRNA turnover. Specifically, it interacts with the heterogeneous ribonucleoproteins hnRNP-I and AUF1 (or hnRNP-D) with opposite effects on their interaction with c-Myc mRNA. Linc-RoR is required for hnRNP-I to bind to MYC mRNA and stabilize it; while its interaction with AUF1 inhibits AUF1 binding to and AUF1-mediated destabilization of MYC mRNA [116]. As a consequence, the half-life of MYC mRNA increases and tumors cells become more proliferative and aggressive. Recently, linc-RoR was also found to be implicated in epithelial to mesenchymal transition (EMT) in ovarian cancer cells through the activation of the WNT/β-catenin pathway, but the exact mechanism has not been elucidated yet [117].

Similarly, the lncRNA CASC11 was characterized as an important diagnostic factor in CRC and was found to promote CRC cell proliferation and metastasis in vitro and in vivo [119]. Mechanistic studies revealed that CASC11 is predominantly localized in the cytoplasm, where it interacts with and stabilizes the heterogeneous ribonucleoprotein K (hnRNP-K) (Fig. 2) [119]. The hnRNP-K protein interacts with β-catenin, GSK-3β and Axin2 proteins and destabilizes the destruction complex, affecting the shuttling of β-catenin between the cytoplasm and the nucleus and its downstream gene expression program [120]. Therefore, CASC11-mediated stabilization of HNRNP-K activates the WNT/β-catenin pathway and promotes tumor progression, invasion and lymph metastasis by activating MYC, CCND1 and MMP7 genes. MYC, in turn binds to the promoter region of CASC11 and enhances its expression through increased promoter acetylation, forming a positive regulatory feed-forward loop that maintains the cancerous phenotype [119].

MYU (c-Myc-upregulated lncRNA) is a direct target of MYC and plays a critical role in MYC-driven proliferation of colon cancer cells [11]. Functional studies upon loss or overexpression of β-catenin, MYC and/or MYU revealed that the WNT/MYC/MYU pathway upregulates the expression of the CDK6 gene, a cyclin-dependent kinase that promotes the G1-S transition of the cell cycle. High levels of MYU were shown to stabilize the expression of CDK6 post-transcriptionally by interacting with the hnRNP-K and suppressing the inhibitory effect of miR-16 on the 3′ UTR of CDK6 (Fig. 2). Concomitantly, the WNT/MYC/MYU-mediated upregulation of CDK6 was found to be essential for cell-cycle progression and tumorigenesis in CRC cells [11].

4.3. LncRNAs interacting with chromatin-modifying complexes

Apart from transcription factors, many lncRNAs are also able to interact with chromatin-modifying complexes recruiting them to specific gene loci to achieve appropriate temporal and spatial gene regulation. Depending on the nature of the chromatin complex, lncRNAs can mediate either activation or repression of their target genes [81]. For example, many lncRNAs have been shown to interact with the polycomb repressive complex (PRC2), which decorates the promoters of its target genes with the H3K27me3 suppressive histone mark. Similarly, other lncRNAs interact with DNA methyltransferases and repress gene expression by increasing DNA methylation. Finally, other lncRNAs interact with H3K4 methyltransferases in order to activate the expression of their target genes [81].

Lnc34a is an example of this class of lncRNAs that negatively regulates the expression of miR-34a by recruiting the DNMT3a/PHB2 and HDAC1 epigenetic regulators to the miR-34a promoter, facilitating DNA methylation and histone deacetylation respectively (Fig. 3) [85]. Its asymmetric distribution during the division of colon cancer stem cells determines the fate of daughter cells; high levels of lnc34a and low levels of miR-34a confer higher proliferative capacity and stemness, while low levels of lnc34a and high levels of miR-34a result in lower proliferative but higher differentiation capability [85]. miR-34a is also involved in this process, by targeting key players of the Notch and WNT signaling pathways, both of which are essential for colorectal cancer stem cell self-renewal [121,122]. As an example, miR-34a has been shown to decrease the expression of the TCF7 transcription factor, attenuating WNT signaling in prostate cancer [122]. Therefore, lnc34a targets miR-34a for cellular control.

On the other hand, the lncRNA NBAT1 (neuroblastoma associated transcript-1) has been shown to function as a tumor suppressor in breast cancer by activating the expression of the DKK1 protein, resulting in WNT pathway abrogation [123]. NBAT1 interacts with the EZH2 catalytic subunit of the PRC2 suppressor complex and represses the deposition of H3K27me3 on the DKK1 promoter, restoring DKK1 gene expression. As a result, NBAT1 inhibits migration and invasion of breast cancer cells by titrating out EZH2 from its target genes, abrogating epithelial to mesenchymal transition [123].

The imprinted lncRNA H19 is abundantly expressed in both

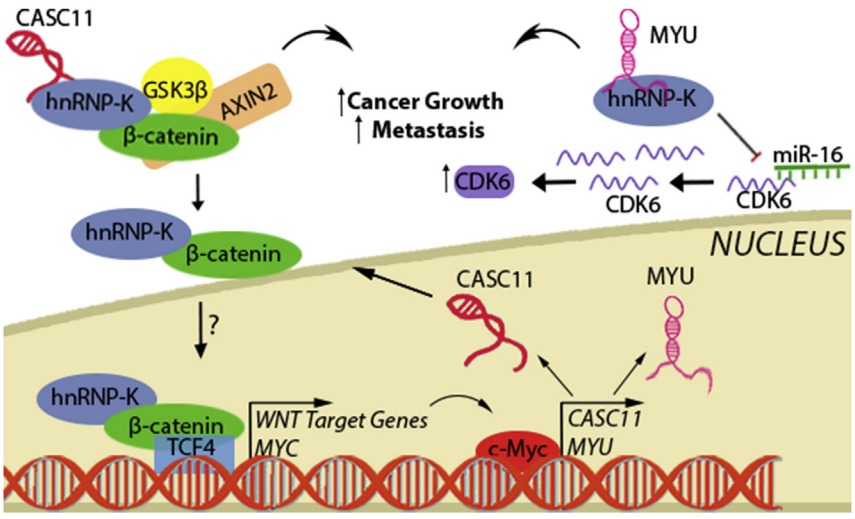

Fig. 2. Several lncRNAs bind to specific combinations of regulatory proteins, potentially acting as scaffold elements within ribonucleoprotein complexes, stabilizing their targets (e.g. CASC11, MYU).

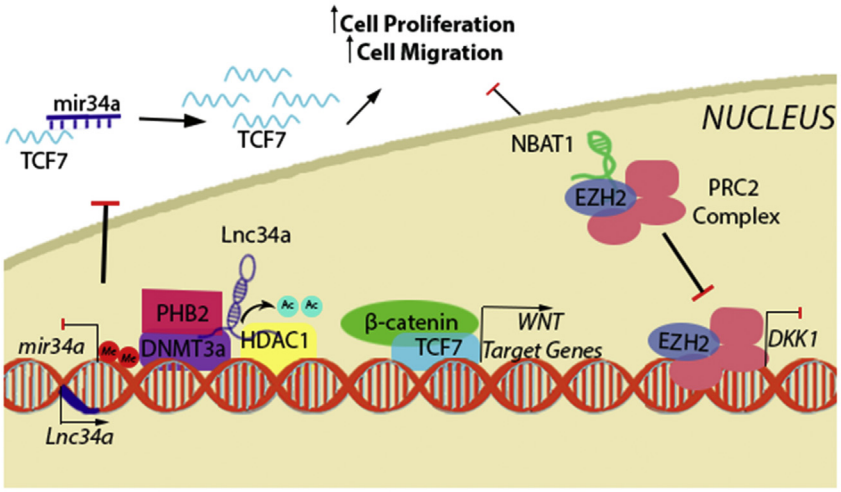

Fig. 3. LncRNAs activate (e.g. NBAT1) or repress (e.g. Lnc4a) gene expression by modulating the recruitment of chromatin-modifying complexes to their DNA targets.

extra-embryonic and fetal tissues and plays a central role in genomic imprinting during growth and development [124]. Its expression is repressed after birth but it reappears in tumors, regulated, among others, by the MYC and ER transcription factors [125–127]. The role of H19 in tumor initiation and progression has long been the subject of controversy, appearing to function as both tumor suppressor (e.g. prostate [128], liver [129] and Wilm's tumors [130]) and oncogene (e.g. breast [131], bladder [132] and colorectal cancer [133]). Upregulation of H19 promotes bladder cancer metastasis in vivo and in vitro by binding to EZH2 and increasing H3K27me3 on several promoters of tumor suppressor genes [132]. For example, NkdI, an antagonist of WNT signaling, is negatively regulated by the H19/EZH2 complex. Downregulation of NkdI results in WNT/β-catenin pathway activation and subsequently decreases the expression of E-cadherin, promoting EMT and increasing the metastatic dynamic of bladder cancer cells [132]. In colon cancer cells, H19 interacts with the macroH2A protein to de-repress the expression of CDK8, CDK4 and CCND1, leading to cell cycle progression [133]. Moreover, the increased CDK4-cyclin D1 complex phosphorylates Rb to disrupt the Rb-E2F1 interaction, leading to E2F1 activation and cancer growth. Concomitantly, the increase of CDK8 activates the expression of β-catenin, enhancing the expression of genes involved in cancer metastasis. All these downstream targets could work synergistically to promote cell proliferation and increase cell motility in CRC [133].

Apart from interacting with chromatin complexes, H19 may also participate in the formation of large ribonucleoprotein complexes [129]. For example, it has been found to function as a decoy for the hnRNP-U protein, inhibiting WNT/β-catenin signaling at the transcriptional level and attenuating cell proliferation of fetal liver cells [129]. In addition, H19 also functions as a molecular sponge (see below), inhibiting let7-mediated down-regulation of c-Myc expression [134]. Moreover, it activates the WNT/β-catenin pathway and promotes osteoblast differentiation by functioning as a competing endogenous RNA for miR-141 and miR-22, both of which are negative regulators of osteogenesis [135]. To sum up, H19 modulates the WNT/β-catenin signaling pathway in several ways to promote or inhibit tumorigenesis and cancer metastasis.

4.4. LncRNAs participating in chromatin looping

The mammalian genome is organized in higher order chromatin

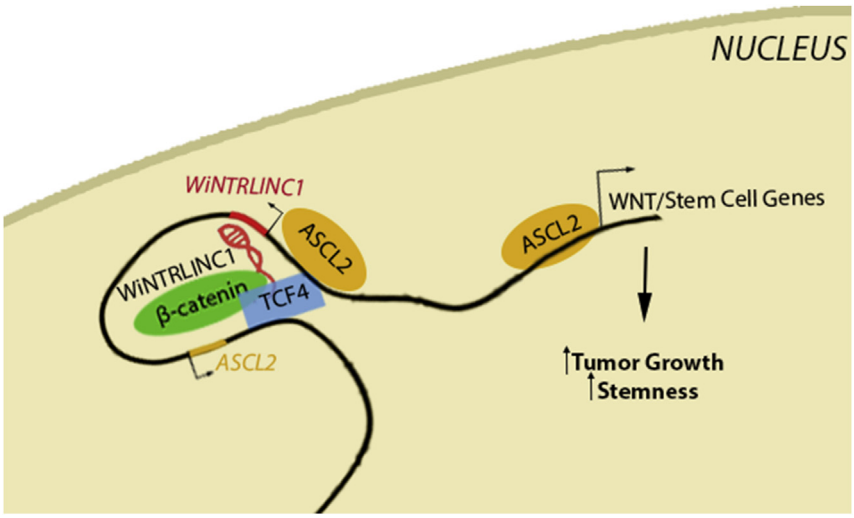

Fig. 4. LncRNAs can regulate gene expression by participating in chromatin looping (e.g. WiNTRLINC1).

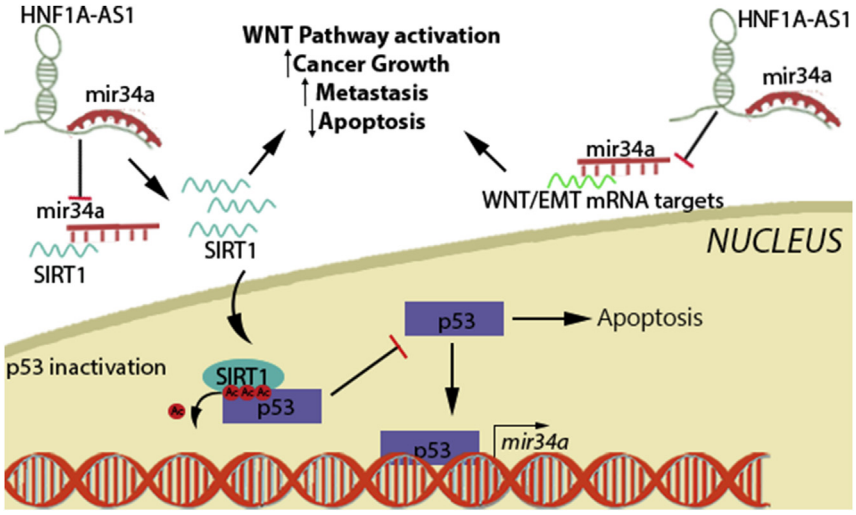

Fig. 5. Several lncRNAs work at the post-transcriptional level as competing endogenous RNAs for microRNAs, titrating microRNA effector complexes away from their mRNA targets (e.g. HNF1A-AS1).

structures, forming intra- and inter-chromosomal loops and membrane-less nuclear compartments, such as speckles and paraspeckles. LncRNAs are increasingly being recognized as essential organizers of this architecture [136,137]. WiNTRLINC1 (WNT-regulated lincRNA1) is a direct WNT/β-catenin target gene that is located in the vicinity of the ASCL2 gene locus and participates in the formation of an intra-chromosomal loop (Fig. 4) [2]. Loss of WiNTRLINC1 results in increased apoptosis and G2-cell cycle arrest in colon cancer cells by decreasing the expression of its neighbor ASCL2 gene, a transcription factor that controls intestinal stem cell maintenance [2]. Chromosome conformation capture experiments (3C) revealed the formation of a chromatin loop bridging the TSS region of WiNTRLINC1 with an enhancer located immediately downstream of the ASCL2 locus. Moreover, the WiNTRLINC1 transcript itself was shown to be required for loop formation and ASCL2 expression affecting recruitment of Pol II, TCF4/β-catenin and the Mediator complex to the ASCL2 regulatory regions. ASCL2, in turn also binds to the WiNTRLINC1 promoter region, activating the expression of WiNTRLINC1 and completing a positive feedback loop. This WiNTRLINC1/ASCL2 regulatory loop is frequently found amplified in patients with colorectal cancer and is positively correlated with worse disease state, increased metastatic rate and decreased patient survival [2]. Thus, aberrant WNT pathway activation increases the expression of WiNTRLINC1 and results in ASCL2 activation, potentially enhancing stemness and carcinogenesis in the intestine.

4.5. LncRNAs functioning as competing endogenous RNAs

Many lncRNAs exert their functions in the cytoplasm. These lncRNAs can regulate gene expression by interfering with protein post-translational modifications, affecting mRNA translation, or acting as decoys for miRNAs and proteins [71]. HNF1A-AS1 (HNF1A antisense RNA 1) is a lncRNA that is involved in the WNT/β-catenin signaling cascade by functioning as a competing endogenous RNA for miR34a in colorectal cancer [138]. HNF1A-AS1 expression is significantly higher in colon cancer patients with advanced stage, lymph node metastasis, vascular invasion and distant metastasis, while its loss significantly impairs the malignant phenotypes of colorectal carcinoma cell lines [138]. Recently, HNF1A-AS1 was revealed to be directly involved in colon cancer progression by competitively binding miR-34a and regulating SIRT1 expression, the protein responsible for deacetylation-mediated p53 inactivation (Fig. 5) [138,139]. Besides promoting apoptosis, miR-34a and p53 are also known negative regulators of the WNT/β-catenin signaling cascade [140]. miR-34a targets a set of highly conserved sites in the 3′ UTR of WNT and EMT genes, such as WNT1, WNT3, LRP6, AXIN2, β-catenin, LEF1 and Snail, resulting in suppression of TCF/LEF transcriptional activity and the EMT program [141]. Consequently, WNT target genes, such as MYC and CCND1, are transcriptionally activated by HNF1A-AS1, promoting the progression of colon cancer [138]. Thus, increased levels of HNF1A-AS1 might play a causative role in colon carcinogenesis and be responsible for increased invasiveness and metastasis of cancer cells.

PTCSC3 (Papillary Thyroid Carcinoma Susceptibility Candidate 3) is another competing endogenous RNA which participates in WNT/β-catenin pathway modulation. This particular lncRNA was firstly identified as an endogenous decoy of miR-574-5p, inhibiting cell growth and promoting cell cycle arrest in thyroid cancer cells [142]. Further studies in papillary thyroid carcinoma (PTC) revealed that PTCSC3 regulates cell proliferation and migration of cancer cells via modulating the WNT/β-catenin signaling cascade [143]. Specifically, it was shown to function as a tumor suppressor gene, since its loss was positively correlated with increased expression of its oncogenic target miR-574-5p [143]. The latter negatively regulates the expression of the SCAI protein, a putative tumor suppressor, which inhibits the migration of tumor cells by controlling MAL/SRF signaling [143,144]. As a result, loss of PTCSC3 in PTC decreases the expression levels of SCAI and transcriptionally activates the WNT/β-catenin pathway, increasing the expression of WNT target genes that promote cancer propagation [143,145]. Furthermore, PTCSC3 has also been found to inhibit the proliferation and invasion of glioma cells by targeting -through unknown mechanisms-the LRP6 receptor and suppressing WNT/β-catenin signaling in brain tumors [146].

Another example of a miRNA sponge is uc.158, an intergenic, 224nt-long, ultra-conserved lncRNA located on chromosome 13 in the mouse and on chromosome 5 in the human genome [147]. Global lncRNA analysis in hepatocellular carcinoma cell lines with active or inactive WNT/β-catenin signaling revealed that the expression of uc.158 was WNT/β-catenin dependent and was only detectable in cancer cells, making it a promising therapeutic target for WNT-dependent carcinogenesis. The same results were also

obtained in vitro upon treatment of hepatic cells with LiCl, a chemical activator of WNT signaling, or with the WNT/β-catenin inhibitor ICG-001, leading to increased and decreased expression of uc.158, respectively [148]. Knock-down of uc.158 in HepG2 cells results in a sub G0-G1 cell cycle arrest, increased cell death by apoptosis and reduced tumor spheroid-based migration. Analysis of uc-158 sequence revealed that it contains binding sites for the pro-apoptotic miR-193b which targets the anti-apoptotic protein Mcl-1 [148]. Therefore, WNT mediated overexpression of uc.158 in liver cancers drives their growth by deregulating the function of miR-193b and decreasing apoptosis [147].

CCAT1-S (colon cancer-associated transcript 1, the Short isoform or CARLo5, cancer-associated region lncRNA5), another lncRNA transcribed from the 8q24 gene desert, is highly expressed in many types of cancer and has been positively associated with poor survival [149–152]. Its expression seems to be highly dependent on the neighbor rs6983267 SNP status, which participates in a long-range chromatin interaction with the CCAT1-S promoter in colon cancer cells [153]. In addition, the expression of CCAT1-S is activated in several tissues by direct binding of MYC on its promoter, promoting cancer cell proliferation, migration and invasion [149–152]. Increased CCAT1-S levels also correlated with high MYC levels, implying that these molecules may upregulate each other and form a positive regulatory feedback loop to enhance gene expression and cancer growth [149–152]. CCAT1-S transcript is enriched in both the nucleus and cytoplasm [154]. The cytoplasmic CCAT1-S was demonstrated to function as a competing endogenous RNA for let-7, upregulating the expression of the latter's target genes, HMGA2 and MYC, and promoting cell proliferation and invasion in hepatocellular cancer [152]. A similar mechanism of CCAT1-S-mediated regulation of MYC expression through sponging let-7 has also been found in lung cancer [151]. Moreover, CCAT1-S has been shown to inhibit myeloid cell differentiation and promote cell proliferation by serving as a competing endogenous RNA for miR-155, altering the expression of its downstream MYC target gene [155]. Beyond regulating the availability of cytoplasmic miRs, CCAT1-S may also affect the expression of miRs by altering their transcription. For instance, nuclear localized CCAT1-S interacts with the EZH2 protein and increases H3K27me3 on the promoter of the tumor suppressor miR-200b gene, augmenting the metastasis of hepatic cancer cells [154].

4.6. Other lncRNAs involved in WNT/β-catenin signaling

Despite the recent progress in research on lncRNAs that are implicated in WNT/β-catenin signaling, there are many such molecules that are modulated by and/or modulate the WNT signaling cascade through still unknown mechanisms. For example, CTD903 lncRNA functions as a tumor suppressor gene and plays protective roles in colorectal cancer [156]. Even though it inhibits WNT/β-catenin signaling and decreases the expression of several downstream WNT target genes, the exact molecular mechanisms by which CTD903 inhibits the WNT pathway remain to be characterized [156]. Moreover, KCNQ1OT1 (KCNQ1 overlapping transcript1), an imprinted antisense lncRNA in the human KCNQ1 locus, is frequently found to be deregulated in colorectal cancers [157]. Although it has been demonstrated that KCNQ1OT1 is a direct transcriptional target of β-catenin, its functional role in WNT-driven colorectal cancers remains unclear [157]. Furthermore, the UCA1 (urothelial carcinoma-associated 1) transcript was shown to negatively affect the expression of the GSK3β protein, activating the WNT pathway through a poorly characterized mechanism and promoting EMT and invasion in breast cancer [158].

5. Concluding remarks

The WNT signaling cascade controls a plethora of biological processes throughout development and adult life of all animals. WNT pathway aberrant activity has been associated with a wide range of pathologies in humans, particularly the development and progression of cancer. Thirty-five years after the identification of the first member of the WNT family, many questions concerning the pathway are still unanswered and the genes that are affected by or modulate the WNT signaling cascade attract significant biomedical interest. Recently, lncRNAs have been found to be regulated by the WNT cascade and to participate in WNT-driven gene expression programs through a plethora of different mechanisms, some of which have been described above. These molecules tend to be expressed in a more tissue-specific and spatiotemporal manner and respond rapidly to various signaling events; this along with their non-coding nature may make them effective biomarkers and novel targets for cancer therapy. We expect that the great advances made in recent years in Next Generation Sequencing (NGS), mass-spectrometry and single-molecule visualization technologies will help uncover more such lncRNAs that intersect the WNT pathway and determine their localization, protein interactors, target molecules and mode of action.

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