Long Non-Coding RNA FENDRR

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The *FOXF1* Adjacent Noncoding Developmental Regulatory RNA (*Fendrr*) plays an important role in the control of gene expression in mammals. It is transcribed in the opposite direction to the neighboring *Foxf1* gene with which it shares a region containing promoters. In humans, *FENDRR* is located on chromosome 16q24.1, and is positively regulated both by the *FOXF1* distant lung-specific cis-acting enhancer and by trans-acting FOXF1. *Fendrr* has been shown to function as a competing endogenous RNA, sponging microRNAs and protein factors that control stability of mRNAs, and as an epigenetic modifier of chromatin structure around gene promoters and other regulatory sites, targeting them with histone methyltrasferase complexes. In mice, *Fendrr* is essential for development of the heart, lungs, and gastrointestinal system; its homozygous loss causes embryonic or perinatal lethality. Importantly, deregulation of *FENDRR* expression has been causatively linked also to tumorigenesis, resistance to chemotherapy, fibrosis, and inflammatory dis-eases.

Keywords: regulatory RNA ; ceRNA ; divergent genes ; lncRNA enhancer ; lung development ; fibrosis ; drug re-sistance

1. Introduction

Nearly the entire human genome is transcribed; however, only approximately 2% of the transcriptome becomes translated into polypeptides longer than 100 amino acids [1][2]. Long non-coding RNAs (lncRNAs) are classified as transcripts of more than 200 nt in length, showing a very limited translational potential. Like mRNAs, most lncRNAs are synthesized by RNA polymerase II and can be capped, polyadenylated, or spliced. LncRNAs have been found in the nucleus and/or cytoplasm. They can functionally interact with microRNAs (miRs), mRNAs, dsDNA, or proteins [3][4].

A subset of anti-sense lncRNAs have their 5′ ends located in proximity to the 5′ ends of the protein-coding genes transcribed in the opposite direction. In some cases, those divergent genes may overlap (e.g., *RNF157-AS1* and *FOXJ1*, *FOXC2-AS1* and *FOXC2*, *ZCCHC14-DT* and *ZCCHC14*). In other cases, like lncRNA gene *FENDRR* (*FOXF1* Adjacent Noncoding Developmental Regulatory RNA; HGNC: 43894, MIM: 614975) and the transcription factor (TF)-coding *FOXF1*, they share a genomic region containing promoters. The symbol *FENDRR* is an acronym for the Fetal-lethal Non-coding Developmental Regulatory RNA and reflects the significance of this lncRNA in early embryonic development [5]. Previously, *FENDRR* was referred to as *FOXF1-AS1*, *lincFOXF1*, *onco-lncRNA-21*, or *TCONS_00024240. FENDRR* was identified in the studies that expanded the catalog of human lncRNAs to over 3000 based on their (i) distinctive histone 3 (H3)-based chromatin signature (H3K4me3-H3K36me3) that marks transcribed genes and (ii) limited protein coding potential [6].

2.*FENDRR* Structure

In humans, *FENDRR* maps to chromosome 16q24.1 at chr16:86,474,529-86,509,099 (GRCh38; ENSG00000268388, RNAcentral: http://rnacentral.org, [7]) (Figure 1A). However, due to a variety of *FENDRR* transcription start sites (TSS) and alternative splicing, the combined genomic region coding for all *FENDRR* transcripts is actually larger, ~37 kb in size, mapping between chr16:86,473,637 for the 3′ end of the *FENDRR:25* transcript and chr16:86,510,615 for the 5′ end of the *HSALNT0234884* transcript (LncBook: http://bigd.big.ac.cn/lncbook, [8]) (Figure 1A,B). Due to the presence of two to six (10 in the *NONHSAT174160.1* isoform) relatively short exons, *FENDRR* isoforms are only ~0.4–4 kb in size after splicing. LncBook, a curated database of human lncRNAs, incorporated in a non-coding RNA database RNAcentral, lists 50 *FENDRR* transcripts (examples are shown in Figure 1A,B). Fourteen of them are annotated in the GENCODE database (http://www.gencodegenes.org, [9]) as *FENDRR-201* to *214* (Figure 1A). The diversity of *FENDRR* splicing contrasts with that of the neighboring protein-coding *FOXF1* gene that features only a single isoform in humans, and supports a contention [10] that non-coding genes undergo alternative splicing more often than the protein-coding genes.

Figure 1. The *FOXF1* Adjacent Noncoding Developmental Regulatory RNA (*FENDRR*) gene, alternatively spliced *FENDRR* transcripts, and promoters. (**A**) GENCODE annotated *FENDRR* isoforms (RNAcentral browser screenshot). (**B**) Selected additional *FENDRR* isoforms listed in RNAcentral. (**C**) Chromatin histone 3 modification, H3K4me3, usually found around active promoters (ENCODE ChIP-seq data from human lung fibroblasts, HLFs). (**D**) Ensembl-annotated promoters (red) and promoter flanking regions (orange). (**E**) ENCODE candidate *cis*-regulatory elements (cCREs, promoters are in red). (**F**) Eukaryotic promoter database (EPDnew)-annotated promoters. (**G**) Compilation of *FENDRR* promoters: EPDnew-annotated, cCRE promoters (red) and cCRE promoter flanking regions (orange). Note that promoter locations correlate with 5′ ends of the majority of *FENDRR* isoforms.

FENDRR has been predicted to have a very low coding capability based on PRIDE reprocessing 2.0 (=0), PhyloCSF score (=65.5245), CPAT coding probability (=28.39%), and Ribosome-profiling: Lee translation initiation sites (=0) and Bazzini small ORFs (=0) predictions (LNCipedia: http://lncipedia.org). In contrast to evolutionary conservation of *FOXF1*, the orthologs of human *FENDRR* are best conserved among higher primates and have not been identified in animals other than mammals (http://genome.ucsc.edu/ENCODE).

3.*FENDRR* Transcription

3.1. Promoter

The chromatin hallmarks of a human promoter include (i) a nucleosome-free region around and upstream of a transcription start site (TSS), (ii) a peak of RNA polymerase II binding slightly downstream of TSS and usually overlapping with the TF binding sites, and (iii) several H3K4me3-marked nucleosomes especially in the downstream portion of the promoter region [11]. Taking into account these criteria, *FENDRR* transcription can start from at least three promoters. The majority of the *FENDRR* isoforms are transcribed from the intergenic promoter P1, annotated in the Eukaryotic promoter database (EPDnew, http://epd.vital-it.ch, [11]) as a promoter element mapping at chr16:86,508,876–86,508,935 and in ENCODE as candidate *cis*-regulatory element (cCRE) mapping at chr16:86,508,968–86,509,250 (Figure 1C–F). This promoter is located within a large island of 365 CpGs and is sensitive to DNA methylation. It belongs to a class of promoters with a dispersed TSS pattern. The emerging view on the functioning of human promoters is that they are intrinsically bi-directional and their actual directionality is controlled both at the transcriptional and/or post-transcriptional levels [12][13][14][15][16]. In support of this notion, an abortive transcription (the *HSALNT0234921* transcript mapping to chr16:86,510,010–86,510,341) originates possibly from this promoter in the direction opposite to the *FENDRR* transcription (Figure 1B). The *FENDRR* promoter with the apparently second highest usage, P2 (EPDnew-annotated element: chr16:86,498,542–86,498,601), is located within *FENDRR* intron 1 and may initiate *FENDRR-202*, *FENDRR:10* to *12*, *26*, *27*, and *29* transcripts (Figure 1). As in the case of the intergenic promoter, the intragenic *FENDRR* promoter P2 is located within an island of 184 CpGs. It is possible that *FENDRR-207*, and *FENDRR:14* to *17* transcripts initiate from two other intragenic promoters located further downstream (Figure 1). Interestingly, one of the *FENDRR* isoforms, the *HSALNT0234884* transcript (chr16:86,474,121–86,510,614), begins with a cCRE (chr16:86,510,620–86,510,824) overlapping the 5′ end of the non-coding portion of the *FOXF1* exon 1 (Figure 1).

3.2. Enhancer

The lung-specific *FOXF1* enhancer is located ~270 kb upstream to the *FOXF1* gene [17][18][19][20][21]. This enhancer was originally described as ~60 kb-large regulatory region based on the overlap of heterozygous copy number variant (CNV) deletions detected in patients with Alveolar Capillary Dysplasia with Misalignment of Pulmonary Veins (ACDMPV, MIM: 265380) due to *FOXF1* haploinsufficiency [17]. It consists of six regulatory elements annotated as enhancers in GeneHancer database [22], each overlapping several cCREs (Figure 2A). In cultured human lung fibroblasts (HLFs) these regulatory elements feature H3K27ac and H3K4me1 chromatin modifications which are the predominant H3 marks at the nucleosomes flanking the active/poised enhancer elements (ENCODE). Moreover, chromosome circular conformation capture (4C) analysis in human pulmonary microvascular endothelial cells and 3C analysis in cells isolated from mouse embryonic lungs showed that this distant enhancer physically interacts with the *FENDRR-FOXF1* intergenic promoter region. Interestingly, we have found a ~35 kb-large genomic instability hotspot, featuring the evolutionarily young LINE1 elements, L1PA2 and L1PA3 flanking five *Alu* repeats, located at the distal edge of this enhancer region, and responsible for several pathogenic enhancer deletions of which the distal breakpoints are mapped within the hotspot [23]. The appearance of this genomic instability hotspot in the course of evolution correlates with the branching out of the *Homo-Pan-Gorilla* clade.

Figure 2. *Cis*- and *trans*-regulation of the *FENDRR* expression in the lungs (modified from [24]). (**A**) *FENDRR-FOXF1* distant enhancer region, located ~250 kb centromerically to the 3′ end of *FENDRR* (UCSC genome browser screenshot). The most essential part of this enhancer is shown in green frame. The enhancer features histone 3 modifications, usually found in active enhancers, and ChIP-seq-determined in HLFs binding sites for numerous transcription factors (TF): FOXA1, FOXP1, CEBPB, MAFK, RAD21, SMARCC1, CTCF, GTF2F1, KAP1, TBP, JUNs, EP300, STAT3, FOS, TFAP2A, and TFAP2C (ENCODE). Single nucleotide variants (SNVs, vertical green lines) that map to the essential part of the enhancer have been proposed to increase activity of the undeleted allele of the enhancer and mitigate ACDMPV phenotype in patients with heterozygous CNV deletions of the enhancer. (**B**) Scheme of mono-allelic expression of *FENDRR* from the paternally inherited chromosome 16 in the presence of a heterozygous CNV deletion of the maternal allele of the *FENDRR-FOXF1* enhancer. The drawing shown is not to scale.

Based on the overlap of additional pathogenic CNV deletions causative for ACDMPV and the presence of hypermorphic single nucleotide variants (SNVs) in the undeleted allele of the enhancer that significantly ameliorated the lethal ACDMPV phenotype by increasing *FOXF1* expression, this enhancer was narrowed to the ~10 kb-large most essential region. This narrowed interval harbors a GeneHancer-annotated regulatory element GH16J086219 (chr16:86,218,986–86,224,837, overlapping with seven cCREs) that corresponds to one of the super-enhancers proposed by Hnisz et al. [25] based on their analysis of the H3K27ac ChIP-seq data from a spectrum of human cell types including fetal lung fibroblasts IMR-90.

Recently, through a correlation of the parental origins of chromosome 16, bearing the heterozygous CNV deletions of this enhancer with that of the transcribed *FENDRR* allele, we have found that the *FOXF1* enhancer regulates *in cis* also *FENDRR* (Figure 2B). This finding may help explain the results of in-depth expression analyses of mouse *Fendrr/Foxf1* and other lncRNA/protein-coding divergent gene pairs showing that lncRNAs mimic the expression patterns of their protein-coding neighbors [26][27].

Besides the *FENDRR/FOXF1* distant enhancer, there are several other regions upstream or downstream to TSS of *FENDRR* (within a large GeneHancer-annotated element GH16J086491) that, based on their H3 chromatin signature and eQTLs (expression quantitative trait loci), may potentially function as *FENDRR* proximal enhancers or modulators of its tissue specificity. For instance, in mice, a genomic region located ~1 kb downstream of *Foxf1* functions as *Foxf1* enhancer in foregut mesoderm and mesenchyme of developing liver and lungs [28]. It was also shown by 3C, using mouse lung cells, that this regulatory element physically interacts *in vivo* with *Fendrr-Foxf1* intergenic region.

3.3. Regulation of FENDRR by FOXF1

In contrast to the co-regulation of *FENDRR* and *FOXF1* expression by the same *cis*-acting distant enhancer, the involvement in this regulation of the *trans*-acting TF FOXF1 was unexpected. Depletion of *FOXF1* in lung fibroblasts by siRNA or *FOXF1* point mutations causative for ACDMPV were found to correlate with a substantial (~50%) decrease in *FENDRR* levels (measured by qPCR with TaqMan assay for the exon 1/2 junction, and RNA-seq, respectively). *Foxf1* was also shown to likely support *Fendrr* expression in mice [29]. However, the binding of *FOXF1* to the *FENDRR* promoters or the enhancer has yet to be documented. Interestingly, *FENDRR* promoters and the enhancer all contain several variants of the FOX TF binding RYAAAYA motif (R = purine, Y = pyrimidine; [30]), suggesting a possibility of direct regulation of *FENDRR* expression by *FOXF1*. In support of this notion, ChIP-seq experiments of the TF binding (ENCODE) showed that other members of the FOX TF family, especially FOXA1, bind to the *FENDRR* major promoter, P1, and the essential region of the enhancer. In addition, *FOXF1* might also indirectly regulate *FENDRR* expression through the control of factors that directly regulate *FENDRR*. Based on our RNA-seq analyses of the ACDMPV transcriptomes, of about 40 TFs potentially interacting, based on ENCODE's ChIP-seq data, with the *FENDRR* primary P1 promoter and the most essential portion of the enhancer, the expression of a histone methyltransferase subunit, ASH2L (binding next to *FENDRR* P1 promoter's cCRE), positively correlates with the expression of *FOXF1* (reduced by ~40% in ACDMPV cases linked to *FOXF1* deficiency). ASH2L can interact with MLL [31] , a Trithorax-group (TrxG) protein involved in histone 3 methylation, H3K4me3, which is usually associated with open chromatin at active promoters. Thus, ASH2L might mediate positive regulation of *FENDRR* expression by *FOXF1*.

3.4. Other Factors Controlling FENDRR Transcription

Another potential regulator of *FENDRR* expression is a pro-apoptotic Annexin 2 (ANXA2) [32]. In electrophoretic mobility shift assay performed using extracts from rat pancreatic acinar cells and fragments of the *Fendrr* promoter, ANXA2 was specifically bound to the *Fendrr* intergenic promoter, and the increase in *Anxa2* expression in caerulein-treated pancreatic cells positively correlated with the increase in the *Fendrr* level.

Using a reporter assay in lung cancer cells lines, *FENDRR* was also shown to be positively regulated by EGR2 and TFAP2A [33]. Both these TFs are known to bind to the *FENDRR* primary promoter based on ChIP-seq data from lung fibroblasts (ENCODE).

Interestingly, induced expression of *Mesp1* during cardiomyocyte differentiation also led to upregulation of several genes including *Fendrr* [34]. Thus, *Fendrr* can be a downstream effector of MESP1, a TF best known as a master regulator of cardiovascular system development.

Regarding suppressors of *FENDRR*, its expression is negatively regulated in the lungs by SMAD3 (but not SMAD2), which is a major signal transducer for cell-membrane Ser/Tyr kinase receptors of TGF-β1 [35]

Of note, using ChIP-seq for TBX2 and TBX4 in IMR-90 fibroblasts, we have found a specific binding of (i) TBX4 at chr16:86,223,833–86,225,160, largely overlapping the GH16J086219 regulatory element in the essential region of the *FENDRR-FOXF1* enhancer, (ii) TBX4 at chr16:86,508,364–86,508,853 next to the *FENDRR* primary promoter, and (iii) TBX2 at 86,507,893–86,509,510, overlapping the *FENDRR* primary promoter [36]. The functional significance of these interactions is currently unknown, but they suggest the existence of a direct regulatory relationship between TBX4-FGF10 and SHH-FOXF1 signaling pathways during lung development.

Lastly, it has been suggested that *FENDRR* expression can be regulated through the epigenetic modification of its promoter (P1) that overlaps a large CpG island. The hypermethylation of this promoter has been shown to correlate with suppression of *FENDRR* expression in gastric cancer-associated fibroblasts [37] Hypermethylation of the *FENDRR* promoter was also found in 36% of non-small cell lung cancers[38] .

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