nucleotide content of the RNA. ADARs are responsible for binding to double stranded RNA (dsRNA) and converting adenosine (A) to inosine (I) by deamination. Inosine is structurally similar to that of guanine (G) which leads to I to cytosine (C) binding. Inosine typically mimicks guanosine during translation. Thus, the conversion from A to I in the RNA disrupts the normal A:U pairing which makes the RNA unstable. Codon changes can also arise from editing which may lead to changes in the coding sequences for proteins and their functions. ADAR also impacts the transcriptome in editing-independent ways, likely by interfering with other RNA-binding proteins.

[0006] In mammals, there are three types of ADARs, ADAR1, ADAR2 and ADAR3. ADAR1 and ADAR2 are found in many tissues in the body while ADAR3 is only found in the brain. Studies have shown that ADAR1 and ADAR2 are frequently dysregulated in cancers. It has been suggested that ADAR1 is responsible for the disrupted A to I editing pattern seen in various cancers. The dysregulation of ADAR1 expression could change the frequency of A to I transitions in the protein coding region of oncogenes or tumor suppressor genes, resulting in mutated oncogene or tumor suppressor gene products which drive the development of cancers.

[0007] As the ADAR proteins have thousands of editing substrates, simply modulating the expression of ADARs may cause considerable off-target effects. Therefore, there is a need for ADAR inhibitors that specifically inhibit the RNA edition of the oncogenes or tumor suppressor genes targeted by ADARs.

SUMMARY

[0008] In one aspect of the present disclosure, there is provided an oligonucleotide targeting the core editing-site complementary sequence (ECS) of *AZIN1* gene, wherein the core ECS of *AZIN1* gene comprises the sequence 5'- GCTTTTCC-3', and wherein the oligonucleotide comprises one or more nucleotides with sugar modification and one or more modified internucleotide linkages. In another aspect, there is provided a pharmaceutical composition comprising the oligonucleotide as disclosed herein. In another aspect, there is provided a method of inhibiting *AZIN1* pre-mRNA editing in a cell, the method comprising contacting the cell with the oligonucleotide as disclosed herein, or the pharmaceutical composition as disclosed herein. In another aspect, there is provided an *ex vivo* or *in vitro* method of inhibiting *AZIN1* pre-mRNA editing in a cell, the method comprising contacting the cell with the oligonucleotide as disclosed herein, or the pharmaceutical composition as disclosed herein. In another aspect, there is provided a method of treating cancer in a subject in need thereof,

comprising administering to the subject a therapeutically effective amount of the oligonucleotide as disclosed herein, or the pharmaceutical composition as disclosed herein, wherein the cancer is associated with *AZIN1* pre-mRNA editing. In another aspect, the present disclosure refers to the use of the oligonucleotide as disclosed herein, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the cancer is associated with AZIN1 pre-mRNA editing.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] The invention will be better understood with reference to the detailed description when considered in conjunction with the non-limiting examples and the accompanying drawings, in which:

[0010] **Figure 1** shows that the 3'end sequence of exon 12 is required for *AZIN1* editing. **Figure 1A** is a schematic diagram of *AZIN1* minigene constructs generated by inserting 5 different fragments (FA, FB, FC, FD or FE) covering the edited exon 11 and flanking exons (exon 10 and 12) and introns (intron 9, 10, 11 and 12) into either pRK7 or pcDNA3.1 vector. The arrow indicates relative position of the editing site. **Figure 1B and 1C** are sequencing chromatograms illustrating editing of endogenous *AZIN1* (Figure 1B, left panel) and exogenous *HTR2C* (**Figure 1B**, right panel) or *AZIN1* (**Figure 1C**) transcripts transcribed from pRK7-based minigene constructs in the HEK293T cells co-transfected with the indicated pRK7 minigenes and empty vector (EV) or *ADAR1* expression construct (ADAR1). **Figure 1D** shows sequencing chromatograms illustrating editing of endogenous and exogenous *AZIN1* transcripts in HEK293T cells co-transfected with pcDNA3.1-based minigenes and EV or *ADAR1*. In **Figure 1B -1D**, percentage of editing is calculated as area of "G" peak over the total area of "A" and "G" peaks. * indicates no editing is detected. Black arrow indicates the position of editing site. **Figure 1E** shows predicted RNA second structure of AZIN1 by RNAfold. An 8-nt sequence indicated by the small arrows on the right are the potential core ECS. Editing site is indicated by the solid arrowhead on the left. Minimum free energy (MFE) structures drawing encoding base-pair probabilities are shown. Base-pair probabilities are shown by a colour spectrum. Taken together, **Figure 1** shows that amongst all *AZIN1* minigenes (using either pRK7-based or pcDNA3.1-based minigene systems), only *AZIN1* transcripts transcribed from the minigene containing fragment A (FA), which lacks 90-bp sequence at 3' end of exon 12, was unable to be edited. This suggests that the ECS of *AZIN1* is located at the 3' end of exon 12.

[0011] **Figure 2** shows that an 8-nt sequence at 3'end of exon 12 is the core ECS and indispensable for *AZIN1* editing. **Figure 2A** is a schematic diagram of FE-1, 2 and 3

Claims:

1. An oligonucleotide targeting the core editing complementary sequence (ECS) of *AZIN1* gene, wherein the core ECS of *AZIN1* gene comprises the sequence 5'-GCTTTTCC-3', and wherein the oligonucleotide comprises one or more nucleotides with sugar modification and one or more modified internucleotide linkages.

2. The oligonucleotide of claim 1, wherein the oligonucleotide is a ribonucleic acid (RNA) oligonucleotide.

3. The oligonucleotide of claim 1 or 2, wherein the oligonucleotide is an antisense oligonucleotide.

4. The oligonucleotide of claim 3, wherein the antisense oligonucleotide is a non-degrading antisense oligonucleotide.

5. The oligonucleotide of any one of claims 1 to 4, wherein the oligonucleotide comprises a sequence complementary to 5'- GCTTTTCC-3'.

6. The oligonucleotide of claim 5, wherein the sequence complementary to 5'-GCTTTTCC-3' is located near the 3' end of the oligonucleotide.

7. The oligonucleotide of any one of claims 1 to 6, wherein the nucleotide with sugar modification is selected from the group consisting of 2′-O-methyl modified nucleotide, 2′-O-methoxyethyl modified nucleotide, 2′-fluoro modified nucleotide, 2',4'-bridged nucleic acid modified nucleotide, locked nucleic acid (LNA) modified nucleotide, and morpholine ring modified nucleotide.

8. The oligonucleotide of any one of claims 1 to 7, wherein the modified internucleotide linkage is selected from the group consisting of phosphorothioate, phosphoramidate, and phosphorodiamidate.

9. The oligonucleotide of claim 8, wherein the oligonucleotide comprises phosphorodiamidate morpholino oligomers (PMOs).

10. The oligonucleotide of any one of claims 5 to 9, wherein at least five nucleotides in the sequence complementary to 5’- GCTTTTCC-3’ are modified with sugar modification.

11. The oligonucleotide of any one of claims 5 to 10, wherein the oligonucleotide comprises at least three modified internucleotide linkages in the sequence complementary to 5’- GCTTTTCC-3’.

12. The oligonucleotide of any one of claims 5 to 10, wherein the oligonucleotide does not comprise any modified internucleotide linkages in the sequence complementary to 5’- GCTTTTCC-3’.

13. The oligonucleotide of any one of claims 1 to 12, wherein at least 50% of the nucleotides are modified with sugar modification.

14. The oligonucleotide of any one of claims 1 to 13, wherein at least 10% of the internucleotide linkages in the oligonucleotide are modified internucleotide linkages.

15. The oligonucleotide of any one of claims 1 to 14, wherein each nucleotide in the oligonucleotide is modified with sugar modification.

16. The oligonucleotide of any one of claims 1 to 15, wherein each nucleotide in the oligonucleotide is modified with sugar modification and is connected to an adjacent nucleotide via a modified internucleotide linkage.

17. The oligonucleotide of any one of claims 1 to 16, wherein the oligonucleotide is of at least 70% identity to the sequence 5'-UUAAGCUUCAGCGGAAAAGC-3' (SEQ ID NO: 5).

18. The oligonucleotide of any one of claims 1 to 17, wherein the oligonucleotide comprises or consists of the sequence 5'-UUAAGCUUCAGCGGAAAAGC-3' (SEQ ID NO: 5).

19. The oligonucleotide of any one of claims 1 to 18, wherein the oligonucleotide is of at least 70% identity to the sequence 5'-mUmUmAmAmGmCmUmUmCmAmGmCmGmGmAmAmAmAmGmC-3' (SEQ ID

NO: 6), 5'-
mU*mU*mA*mA*mG*mC*mU*mU*mC*mA*mG*mC*mG*mG*mA*mA*mA*
mA*mG*mC-3' (SEQ ID NO: 7), 5'-
mU*mU*mA*mA*mG*mCmUmUmCmAmGmCmGmGmAmAmAmAmGmC-3'
(SEQ ID NO: 8), or 5'-
mUmUmAmAmGmCmUmUmCmAmGmCmGmGmA*mA*mA*mA*mG*mC-3'
(SEQ ID NO: 9), wherein m represents 2'-O-Me sugar modification, and * represents phosphorothioate linkage.

20. The oligonucleotide of any one of claims 1 to 11, wherein the oligonucleotide comprises or consists of a sequence selected from the group consisting of 5'-mUmUmAmAmGmCmUmUmCmAmGmCmGmGmAmAmAmAmGmC-3' (SEQ ID NO: 6), 5'-
mU*mU*mA*mA*mG*mC*mU*mU*mC*mA*mG*mC*mG*mG*mA*mA*mA*
mA*mG*mC-3' (SEQ ID NO: 7), 5'-
mU*mU*mA*mA*mG*mCmUmUmCmAmGmCmGmGmAmAmAmAmGmC-3'
(SEQ ID NO: 8), and 5'-
mUmUmAmAmGmCmUmUmCmAmGmCmGmGmA*mA*mA*mA*mG*mC-3'
(SEQ ID NO: 9), wherein m represents 2'-O-Me sugar modification, and * represents phosphorothioate linkage.

21. A pharmaceutical composition comprising the oligonucleotide of any one of claims 1 to 20.

22. An *ex vivo* or *in vitro* method of inhibiting *AZIN1* pre-mRNA editing in a cell, the method comprising contacting the cell with the oligonucleotide of any one of claims 1 to 20, or the pharmaceutical composition of claim 21.

23. The method of claim 22, wherein the *AZIN1* pre-mRNA editing is mediated by adenosine deaminase acting on RNA-1 (ADAR-1).

24. Use of the oligonucleotide of any one of claims 1 to 20, or the pharmaceutical composition of claim 21 in the manufacture of a medicament for treating cancer in a

subject in need thereof, wherein the cancer is associated with *AZIN1* pre-mRNA editing.

25. The use of claim 24, wherein the cancer is selected from the group consisting of hepatocellular carcinoma (HCC), esophageal squamous cell carcinoma (ESCC), non-small cell lung cancer (NSCLC), and colorectal cancer (CRC).

26. The use of claim 24, wherein the cancer is liver cancer.

27. The use of any one of claim 24 to 26, wherein the use further comprises measuring the level of edited *AZIN1* pre-mRNA in a sample obtained from the subject, prior to when the oligonucleotide of any one of claims 1 to 19, or the pharmaceutical composition of claim 20 is to be administered.

28. The use of claim 27, wherein the level of edited *AZIN1* pre-mRNA is at least 15% higher as compared to the level of edited *AZIN1* in a sample obtained from a healthy subject.