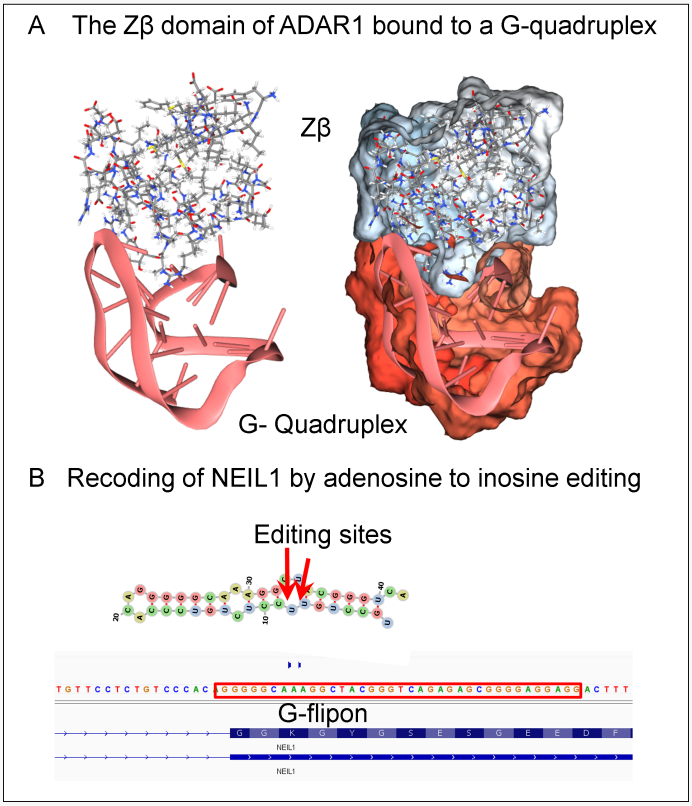
G-Flipons promise to improve the therapeutic efficacy of RNA editing

The paper resolves many unanswered questions about the recoding of RNAs by ADAR1 and the outcomes produced in a cell



ADAR1 Zβ bound to a G-quadruplex. RNA editing by ADAR1 improves the performance of the DNA repair protein NEIL1. Recoding is likely facilitated by the G-quadruplex that localizes ADAR1 to this site.

CHARLESTOWN, MA, UNITED STATES, March 11, 2025 /EINPresswire.com/ -- The double-stranded RNA editing enzyme ADAR1 offers excellent promise for editing RNAs to correct genetic mutations and to alter protein interactions that lead to disease. The enzyme also regulates innate immune responses to cancer. In a study just published, a new mechanism of regulating this enzyme is revealed that can be translated rapidly to the clinic.

ADAR1 connects two forms of genetic programming, one based on codons and the other on flipons. ADAR1 can edit codons in RNA messages to change specific amino acids in proteins. The recoding occurs after the RNA is made. The editing corrects errors without any change to DNA. ADAR1 also plays essential roles in preventing immune responses against self-RNAs in normal cells. These outcomes are regulated by flipons that change conformation when viruses attack the cell or become cancerous.

ADAR1 has a Zα domain that recognizes left-handed Z-DNA and Z-RNA (collectively called ZNA), a function vital to stopping inflammatory responses directed at self RNAs—the form of this protein with the Zα domain shuttles throughout the cell to prevent false alarms. ADAR1 also has a Zβ domain that does not bind ZNA. The function of Zβ has long remained mysterious.

The paper reports strong evidence that Zβ binds to another flipon conformation called a G-

quadruplex. This structure is formed by repeat sequences rich in guanosine. These segments fold into a four-stranded quadruplex structure (Figure). The fold occurs as RNA is made by the RNA polymerase, allowing ADAR1 to latch rapidly onto the RNA. ADAR1 then directs how that particular RNA is handled – whether it is edited, triaged, or processed normally. In these situations, the G-quadruplexes play an informational role. They signal that action is needed and identify those transcripts likely to cause further problems.

Flipons help ADAR1 correctly compile the codons. By changing shape, they act as binary switches to initiate one outcome or another. The findings from the paper suggest that G-flipons might help ADAR1 more efficiently edit RNAs in several diseases. The G-quadruplex forming sequences can be easily incorporated into the RNA editmers that direct the recoding of messages.

This study involved a collaboration with Drs. Terry Lybrand and Martin Egli at Vanderbilt Medical School, Oleksandr Cherednichenko, and Dr. Maria Poptsova at HSE University. Alan Herbert at InsideOutBio led the team.

About InsideOutBio: InsideOutBio is a start-up focused on developing a novel class of proprietary therapeutics to 'light' up tumors for the immune system to kill by reprogramming self/nonself pathways within cancer cells. Dr. Herbert leads discovery at InsideOutBio. His work on Z-DNA was foundational to the discovery of flipons. These statements about InsideOutBio comply with Safe-Harbor laws. They are forward-looking and involve known and unknown risks and uncertainties. They are not guarantees of future performance and undue reliance should not be placed on them.

Alan G Herbert
InsideOutBio, Inc
+1 617-584-0360
email us here
Visit us on social media:
X
