Deciphering the intricate structure and dynamic behavior of the minimal HDV-like ribozyme Drz-Mtgn-1

S. Jana[1], S. Johannsen[1], R. Sigel[1]*

[1]University of Zurich, Department of Chemistry, Winterthurerstrasse 190, 8057 Zurich

Hepatitis delta virus (HDV)-like ribozymes are a class of small self-cleaving RNAs spread across different life forms and play crucial roles in various biological processes [1]. The self-cleavage reaction relies on an acid-base mechanism in which a conserved cytosine in the catalytic core activates the 2'-hydroxyl group adjacent to the phosphodiester bond for nucleophilic attack. Although ribozymes in this family vary widely in length, nucleotide composition, and cleavage rates, they all share the same nested double pseudoknot structure that resembles the prototypical HDV ribozyme. While the HDV ribozyme has been extensively studied regarding its structure, catalytic mechanisms, and biological significance, the same level of understanding is still lacking for most group members. However, this knowledge is essential to identify the structural elements and specific nucleotides that tune the dynamics and, thus, the catalytic reaction of this ribozyme family.

Here, we study the ribozyme Drz-Mtgn-1, which is derived from the human gut microbiome and exhibits a unique bell-shaped self-cleavage activity in the presence of divalent metal ions. This ribozyme belongs to the minimal HDV-like ribozymes lacking a non-essential catalytic activity domain [3]. Our goal is to determine the three-dimensional structure of Drz-Mtgn-1 and decipher its complex interplay with metal ions using NMR spectroscopy. Initial NMR studies reveal that Drz-Mtgn-1 ribozyme folds into the nested double pseudoknot structure, even without divalent metal ions. In the next step, we aim to localize specific metal ion binding sites using chemical shift change experiments, paramagnetic line broadening studies, and direct detection of NOE contacts between RNA and metal probes.

This study will shed light on the structural basis, and the role of metal ions in the dynamics of the self-cleavage reaction and help connect the gap regarding ribozyme's structure and function.

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