One RNA Aptamer Sequence, Two Structures: A Collaborating Pair that Competitively Inhibits AMPA Receptors

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Both theoretical and experimental work demonstrated that a single RNA sequence can assume multiple, distinctly folded structures with different functions. These structures, or more precisely conformations, are different structural folds that can be reversibly generated through unfolding/refolding. For example, the same RNA sequence can adopt a fold that catalyzes RNA cleavage or a different fold that catalyzes RNA ligation. On binding of small metabolites, riboswitches can switch their conformations and consequently functions. However, here we show that a single RNA sequence assumes two structures with two different functions, both of which are required to work together in order to competitively inhibit the GluR2 AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor with an IC_{50} value of ~30 nM. Yet, the two structures, once formed during *in vitro* transcription, are not interconvertible through unfolding or denaturation/refolding. The sequence we present corresponds to an aptamer, which was identified from systematic evolution of ligands by exponential enrichment (SELEX) against the GluR2 receptor from an RNA library. GluR2 is an AMPA receptor subunit of the glutamate ion channel family, and plays a key role in brain development and function. Excessive activity of the GluR2 AMPA receptors has been implicated in a number of neurological disorders, and therefore inhibitors, such as RNA aptamers, might be useful as pharmacological tools. To understand the RNA structure-function relationship, we have carried out, and describe here, a series of experiments, including in-line probing, chemical labeling and enzymatic digestion, to demonstrate that these RNA species have the same sequence, but are structurally and functionally distinct. Our results suggest more broadly that natural RNA molecules that show structural dissimilarities with different functions can nevertheless share a common ancestry and bear the same evolution memory.