New Data Science in Nucleic Acids Chemistry (13): Global and local molecular crowding effects depending on the size of crowding cosolute on stability of pseudoknot RNA

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RNA pseudoknot (PK) is a common motif in functional RNAs. Intracellular functions of RNAs are expected to depend on the stability of their high-order structures, in which stabilities differ depending on molecular environments. We have demonstrated that crowding cosolutes, composed of diverse small and large molecular sizes, significantly alter the thermodynamic properties of RNA structures.[1] Understanding how these crowding cosolutes influence PK stability is essential for deciphering contribution of PK structures involved in RNA functions.

In this study, we evaluated the impact of the crowding cosolutes on PKs stability, focusing on their S2 stem region, which formation differentiates PK structure from simple hairpin conformer. Polyethylene glycol (PEG) with different average molecular weights of 200 (PEG200) and 8000 (PEG8000) were employed to mimic the crowding environments. Studies using PK variants containing abasic sites on a loop, revealed distinct stabilization mechanisms depending on the size of the crowding cosolutes. The nucleobases in the loop region destabilized the S2 stem under diluted conditions by disturbing hydration required to be stabilized.[2] Local stabilization of S2 stem region was observed in the presence of PEG200 through diminished destabilizing effects caused by the nucleobases in the loop region. On the other hand, PEG8000 exerted a global stabilizing effect by promoting the compact PK conformation via excluded volume effects (Fig. 1).[3] The results in this study provide critical insight and serve as a bridge between the diverse structural characteristics of PKs and mechanisms of their functionalization in varying cellular contexts.

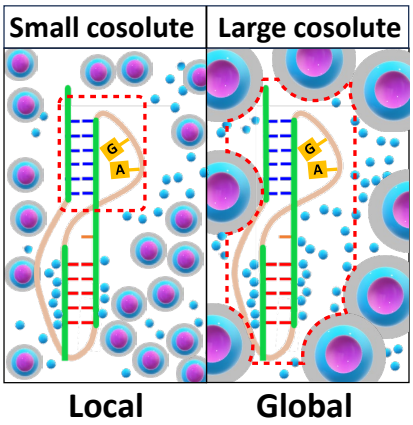

Fig. 1 Distinct stabilization mechanisms caused by small and large crowding cosolutes.

1) T. Endoh, H. Tateishi-Karimata, and N. Sugimoto, in ***Handbook of Chemical Biology of Nucleic Acids***, ed. N. Sugimoto, Springer Nature Singapore, Singapore, (2022), DOI: 10.1007/978-981-16-1313-5_40-1, pp. 1-45. 2) S. Satpathi, T, Endoh, N. Sugimoto, *Chem*. Commun., **2022**, *58*, 5952. 3) S. Satpathi, T, Endoh, N. Sugimoto, *Med. Chem. Res.*, **2024**, *33*, 2079.