Nucleic Acids Chemistry beyond the Watson-Crick Double Helix (76) : Structure-based derivatization of berberine to improve the potency for targeting RNA structures

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Identification of RNA motifs interacting with natural phytochemicals (PCs) is a challenging process due to the absence of a distinctive binding pocket in RNA, unlike protein. In this regard, we have developed a unique material namely, RNA-capturing microsphere particles (R-CAMPs),[1] and have identified the RNA structure motif interacting with berberine (BRB) from the transcriptome library of HeLa cells. Detailed interaction analysis between BRB and RNA through NMR and other PC analyses showed that the motif is consisting of a cytosine bulge with U-A and G-U closing base pairs for interaction with BRB.[2] In this study, based on the tertiary structure of the RNA/BRB complex, BRB-PEG-Gua, in which one of the -OCH_3 groups of BRB has been chemically modified by a guanidine moiety through an extended ethylene glycol linker, was synthesized to improve the binding affinity to the target RNA. The fluorescence study of BRB-PEG-Gua titrated with RNAs showed improved binding affinity compared to unmodified BRB (Figure). Thermodynamic analyses of RNA in the absence and the presence of BRB-PEG-Gua exhibited an enthalpically-driven stabilization of RNA. The stabilization is expected due to the improved electrostatic interaction between positively charged guanidine moiety and negatively charged phosphate on the RNA backbone. Chemical modification of PCs based on the structure information complexed with RNA enhances the potency of the chemicals derived from PCs toward functional RNAs that would be a crucial aspect for developing the RNA-targeting therapeutics.

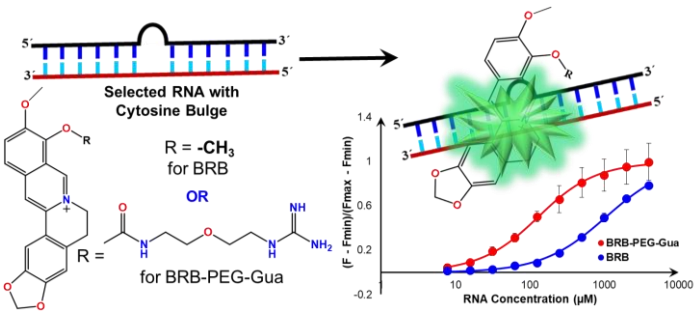

Figure. Schematic representation of improved RNA binding affinity by BRB modified with guanidine moiety (BRB-PEG-Gua).

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