Structure-Function Guided Fabrication of Biodegradable RNA-Binding Polymers

Moran Frenkel-Pinter[1]

[1] Institute of Chemistry and Center for Nanoscience and Nanotechnology, The Hebrew University of Jerusalem, 91904 Israel

moran.fp@mail.huji.ac.il

Development of biodegradable polymers that bind and stabilize RNA is of high importance for various pharmaceutical and biotechnological applications. For instance, the ability to control the degradation rates of RNA is crucial for development of RNA-based vaccines (such as latest developments of coronavirus vaccines). Depsipeptides, which contain both peptide and ester bonds, have been widely studied as biodegradable polymers and as natural products, and are known to synergize from the properties of both peptides and polyesters. While interactions between RNA and positively charged peptides have been previously investigated, no comparable studies on interactions between positively charged depsipeptides and RNA have been reported. To study the structure-function relationship of depsipeptide interactions with RNA, we synthesized a library of positively charged depsipeptides and peptides. The sequences varied in the side chains and in the number and location of ester linkages within the depsipeptide backbone. We demonstrated that positively charged depsipeptides significantly increased the thermal stability of folded RNA structures. In turn, RNA can reduce the rate of hydrolysis of positively charged depsipeptide ester bonds by >30-fold. These results suggest that rational design of positively charged depsipeptides can allow tremendous control over the mode of interaction and stability of RNA-peptide complexes.

References

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