Structure-function guided fabrication of biodegradable polymers

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Abstract

Peptides are biologically derived molecules that are widely used in a variety of applications, such as therapeutics, catalysis, cosmetics, and as food additives. Depsipeptides, which are polymers composed of both ester and peptide linkages (Fig. 1A), are peptide analogs and are known to be non-toxic and degradable both in vitro and in vivo, thus synergizing from the combined property of both peptides and esters. Their amide groups allow the establishment of strong intermolecular hydrogen-bond interactions, which enhance their mechanical and thermal properties, while allowing controlled biodegradability due to the presence of easily hydrolyzable ester groups. Indeed, depsipeptides have already shown great promise for biomedical applications such as tissue engineering and drug delivery. More recently, we have shown that cationic depsipeptides bind to and stabilize nucleic acid, properties which can be utilized for controlled drug release and controlled degradation rates.

It has been recently demonstrated that depsipeptides can form spontaneously under mild conditions during drying of mixtures of hydroxy acids and amino acids. Ester linkages diminish kinetic barriers to amino acid condensation by lowering activation energies for the formation of amide bonds through the process of ester-amide exchange (Fig. 1B). However, it was unknown whether depsipeptides form assemblies in an aqueous environment similarly to peptides and proteins. To test the assembly propensity of different depsipeptide backbones, we synthesized depsipeptides using a matrix of eight alpha- and beta- hydroxy acids and six alpha-, beta-, and gamma- amino acids. The reaction products were analyzed by microscopy and a physical stability analyzer to study assembly formation as well as various analytical techniques for chemical analysis.

Our results demonstrate assembly formation in depsipeptide systems containing hydrophobic hydroxy acids and indicate that depsipeptide assemblies containing alpha hydroxy acid backbones are significantly more stable than beta analogs. We now utilize these novel peptide-like molecules to study their potential biological activities, such as antimicrobial activity and enzymatic functions. We expect this research to pave the way for developing potent novel biodegradable drugs using green chemistry approaches.

References

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[2] Frenkel-Pinter M, Haynes JW, Mohyeldin AM, C M, Sargon AB, Petrov AS, Krishnamurthy R, Hud NV, Williams LD* and Leman LJ* (2020). Mutually Beneficial Interactions Between Proto-Peptides and RNA. Nature communications; 11(1):3137. doi: 10.1038/s41467-020-16891-5

Figures

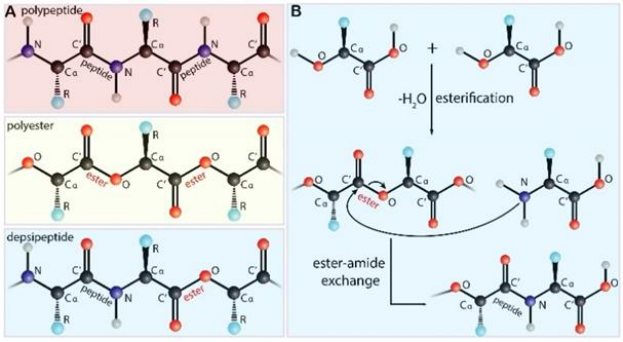

Figure 1. A) Polypeptide, polyester and depsipeptide. B) Depsipeptide formation is preceded by an ester that undergoes ester-amide exchange. Ester-amide exchange, shown here, is one of the possible mechanisms of polymer shuffling.

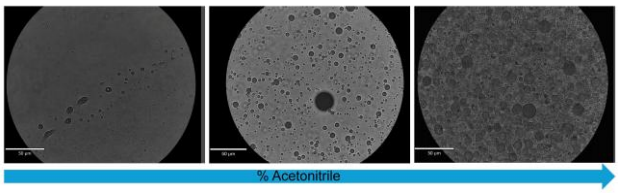

Figure 2. Solvent effect on structure formation of products resulting from dry-down of lactic acid and glycine for one week at 85 °C as evident in bright field microscopy imaging. Different ratios of water:acetonitrile solutions were used to resuspend the dry samples.