Elucidating the impact of polymer structures on insulin activities using synthetic discrete polymers.

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Polymer-protein conjugates have been widely used to improve the stability and pharmacokinetics of therapeutic proteins. However, conventional methodology to generate such conjugates generally involves reactions between disperse polymers and proteins with various modification sites, which results in a heterogenous mixture of the final product. Therefore, these methods lead to inconsistency of manufacturing products among batches, nor providing sufficient capability to study the structure-property relationship between polymers and proteins. Here we show an approach to create a new series of uniform polymer-protein conjugates through an azide-alkyne cycloaddition reaction between a site-specific modified protein, insulin, and different discrete macromolecules synthesized via iterative exponential growth (IEG) strategy. These discrete conjugates eliminate manufacturing variables originating from polymer dispersity and exhibit precise control over the molecular features of their conjugated polymers, such as stereo-configurations of polymer backbone and the structural space between stereo-centers. With this discrete conjugation platform in hand, we can further study the impact of polymer structures on insulin activities. We believe that these fundamental studies offer a new toolbox for the design of future protein-polymer conjugates and represent a step forward towards solving a longstanding challenge of precisely tuning biomaterial properties with high reproducibility.