Glycopolymer–Lectin Interactions and Inhibition of Pathogens using Multivalent Scaffolds

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Background

Protein-carbohydrate interactions mediate a multitude of critical biological recognition processes. The proteins responsible for deciphering this information are termed lectins.

Comparison of Surface Binding with Inhibitory Activity

Glycopolymer–Lectin Interactions

The nature of the interactions between glycopolymers and lectins, and the structural features necessary to obtain high-affinity materials are not fully understood. In this study, we probed multivalent interactions in the α-mannose - Concanavalin-A (ConA) pairing:

- Post-polymerisation Modification: α-β-mannose was ‘clicked-on’ to a poly(propargyl methacrylate) backbone.
- Polymer Chain Lengths: 2 (P1), 6 (P2) and 11 nm (P3).
- Binding inhibition was assessed using Quartz-crystal microbalance with dissipation monitoring (QCM-d) and Fluorescence-linked sorbent assay (FLSA).
- Higher binding affinity = increased mass of glycoside binding to the lectin surface. This property is used to screen new inhibitors.

Inhibition of Bacterial Toxins

Bacterial Toxin Binding

The cholera toxin (CTx) secreted by Vibrio cholerae binds glycosides expressed on the cell surface. Materials with high-affinity and selectivity for these lectins could find applications as anti-adhesive agents.

Tandem Post-Polymerisation Modification

‘Clickable’ units are not compatible with controlled radical polymerisation. Instead, tandem-post polymerisation modification are performed.

- Poly(pentafluorophenyl methacrylate) for easy modification.
- β-galactose was ‘clicked-on’ to pendant alkyne moieties.
- Results in biocompatible methacrylamide based (copolymers).

Role of Linker Length and Carbohydrate Density

- Polymers synthesised with ~ 6 Å (short) and 16 Å (long) linkers.
- Linker length has no effect on PNA inhibition (A).
- Longer linker has 2 – 3 fold lower MIC compared to shorter linker in inhibiting CTx (B).
- 100 X more active than free galactose.

Inhibitors have to be developed from same chain length distribution.

Summary

- Tandem post-polymerisation modification allows synthesis of polymers from same chain length distribution.
- Longer linker has better binding site accessibility.
- Carbohydrate density has an effect.
- Inhibitors have to be developed for the binding site.

References