Design and Synthesis of Antifreeze Glycoproteins and Mimics

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One of the major impediments to detailed studies of AFGPs has been the lack of access to pure samples from natural sources, and no reliable and efficient method of producing pure AFGP glycoforms using chemical synthesis, protein expression techniques or chemo-enzymatic approaches. We recently reported the application of native chemical ligation followed by cysteine desulfurisation to generate pure AFGP glycopeptide analogues of discrete length [1]. We chose native chemical ligation to construct the desired glycopeptides as the method has proved to be extremely reliable for the preparation of peptides and proteins, with and without post-translational modifications.

In terms of the design of functional AFGP mimics, the requirement for a high degree of flexibility of the AFGP structure presents some challenges and opportunities [2]. High conformational flexibility can be achieved with numerous peptidomimetic backbones that are suitably functionalised with sugars. However, the flexibility makes it difficult to understand the subtle structure-activity relationships [3] with respect to the sugars and how to position appropriate hydrophobic groups to both stabilise given conformation(s) and contribute to the energetics of interacting with ice/water and thermal hysteresis. While AFGPs can adopt a conformation in which the disaccharide chains are aligned on one side, creating hydrophobic and hydrophilic faces [3], there is no evidence to support that this conformation is critical to antifreeze activity. The recent report of cyclic AFGPs [4] suggests that the design of constrained cyclic mimics that force the disaccharides, or equivalent hydroxylated functionality, to align and present hydrophilic and hydrophobic faces may provide insights into these interactions as well the interesting profiles of activities exhibited by cyclic AFGPs.

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