Chemical Synthesis of homogeneous glycoforms of human Saposin A

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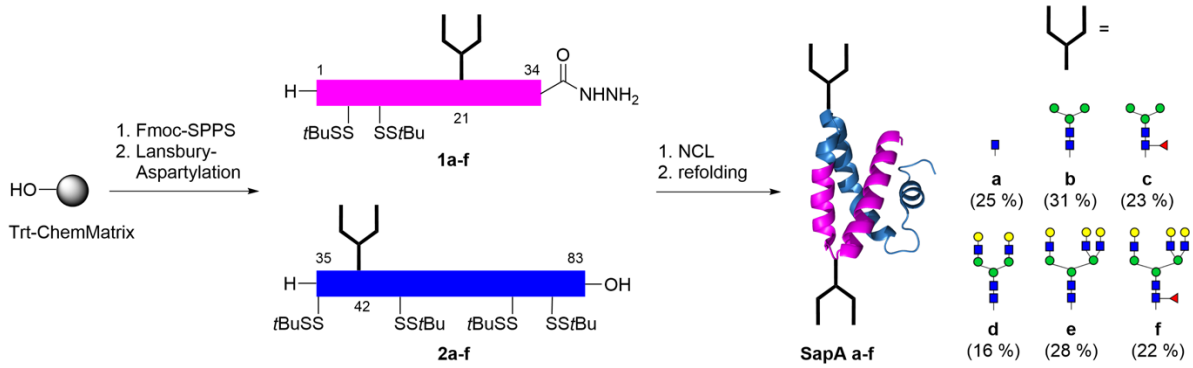
The four sphingolipid activator proteins saposin A-D are a family of small glycoproteins involved in the degradation of sphingolipids in the lysosome.[1] Saposin A (SapA) aids the degradation of galactosylceramide by β-galactocerebrosidase (GALC).[1] Its mechanism of action was revealed by a crystal structure of a dimeric $GALC_2SapA_2$ complex.[2] SapA is also known to form soluble lipid complexes (nanodiscs).[3] However, most studies were conducted with unglycosylated SapA and the role of its glycosylation is not yet well understood. The tendency of synthetic SapD glycoproteins to form soluble SapD-lipid complexes was found to be carbohydrate-dependent.[4] Here we show the synthesis of homogeneous glycoforms of human SapA. The solid phase synthesis of the two glycosylated SapA segments **1** and **2** was challenging requiring special conditions to achieve complete couplings. The glycopeptides (**1a-f** and **2a-f**) were obtained by pseudoproline-assisted Lansbury aspartylation using synthetic N-glycan azides[5] corresponding to the SapA glycans from Gaucher patients.[6] After thioesterification of **1a-f** both segments were ligated by native chemical ligation (NCL) and folded to the desired glycoforms (**SapA a-f**). Currently we are investigating the formation of supramolecular complexes of SapA glycoforms with glycosphingolipids.



Synthesis of SapA a-f glycoforms.

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