Synthesis of a BSA-Le(x) glycoconjugate and recognition of Le(x) analogues by the anti-Le(x) monoclonal antibody SH1: The identification of a non-cross reactive analogue

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Abstract	A Le(x) trisaccharide functionalized with a cysteamine arm was prepared and this synthesis provided additional information on the reactivity of N-acetylglucosamine O-4 acceptors when they are glycosylated with trichloroacetimidate donors activated with excess BF3 center dot OEt2. In turn, this trisaccharide was conjugated to BSA lysine side chains through a squarate-mediated coupling. This BSA-Le(x) glycoconjugate displayed 35 Le(x) haptens per BSA molecule. The relative affinity of the anti-Le(x) monoclonal antibody SH1 for the Le(x) antigen and analogues of Le(x) in which the D-glucosamine, L-fucose or D-galactose residues were replaced with D-glucose, L-rhamnose and D-glucose, respectively, was measured by competitive ELISA experiments. While all analogues were weaker inhibitors than the Le(x) antigen, only the analogue of Le(x) in which the galactose residue was replaced by a glucose unit showed no binding to the SH1 mAb. To confirm that the reduced or loss of recognition of the Le(x) analogues by the anti-Le(x) mAb SH1 did not result from different conformations adopted by the analogues when compared to the native Le(x) antigen, we assessed the conformational behavior of all trisaccharides by a combination of stochastic searches and NMR experiments. Our results showed that, indeed, the analogues adopted the same stacked conformation as that identified for the Le(x) antigen. The identification of a trisaccharide analogue that does not cross-react with Le(x) but still retains the same conformation as Le(x) constitutes the first step to the design of a safe anti-cancer vaccine based on the dimeric Le(x) tumor associated carbohydrate antigen. (C) 2010 Elsevier Ltd. All rights reserved.
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