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Opinion

Relevance of Sulfotopes in the Antigenic Structural Glycoconjugates of Trypanosoma Cruzi, the Causal Agent Of Chagas Disease, Identified by UV MALDI-TOF Analysis

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ABSTRACT

Trypanosoma cruzi, causal agent of Chagas Disease (CD), contains a major antigen, Cruzipain (Cz) with a C-Terminal Domain (C-T) bearing several post-translational modifications. In addition to Cz, the presence of sulfated oligosaccharides was also demonstrated by UV-MALDI-TOF analysis in a minor antigen with Serine-Carboxypeptidase (SCP) activity, as well as in lipidic sulfatides. In Trypanosomatids, sulfate-containing glycoproteins showed to be targets of specific immune responses. Individuals that are chronically-infected by T. cruzi mounted specific humoral immune responses to sulfated-Cz. In absence of infection, C-T-immunized-mice, but not those immunized with sulfate-depleted-C-T, showed surprising ultra-structural heart pathological effects. Additionally, the synthetic anionic sugar conjugate NAcGlc6SO_3 mimics the N-glycan-linked sulfated epitope (sulfotope) humoral response. Strikingly, the participation of sulfotopes in the immunomodulation by host-parasite interaction via Sialic-Acid-Ig-Like-Specific-Lectins (Siglec) binding to sulfosialylated glycoproteins has been reported. Also, recent evidences involved to sulfotopes and their specific antibodies in the immunopathogenesis and infection processes of the experimental CD. Interestingly, sera from chronically T. cruzi-infected individuals with mild disease displayed higher levels of IgG2 antibodies specific for sulfated glycoproteins and sulfatides compared with those in more severe forms of the disease, suggesting their potential use as surrogate biomarkers of disease progression.

Keywords: Trypanosoma cruzi; Cruzipain; C-terminal; Serinecarboxipeptidase; Sulfatides; UVMALDI-TOF-mass spectrometry; Immunomodulation, Immunopathogenesis, Infection, Sulfotopes; Sulfoantibodies; Surrogate biomarker.

BACKGROUND

American Trypanosomiasis or Chagas disease denotes a major endemic health problem and remains to be endemic in large areas of Latin America. The causal agent is the parasitic protozoan Trypanosoma cruzi that presents a complex biological cycle with different developmental forms in accordance to the adaptations essential for living in a triatomine insect vector and a mammalian host. At present, the number of infected people worldwide projected by the World Health Organization sums to 8 million people, and the increase in migratory flow has made to this neglected disease as an emergent public health problematic in non-endemic countries converting it in a global pathology [1,2]. About 30 % of infected individuals, will develop from mild to severe cardiac alterations and it is a common cause of fatal dilated cardiomyopathy, while intestinal compromise is less frequent [3]. T. cruzi contains major and minor antigenic sulfated glycoproteins. In the major antigen, Cz, its C-T is responsible for the immunogenicity of the molecule in natural and experimental infection. We have determined for the first time the presence of sulfated oligosaccharides and that sulfate-bearing glycoproteins in Trypanosomatids are targets of specific immune responses. Moreover, we showed that subjects chronically infected with T. cruzi mount specific humoral immune responses to this sulfated glycoprotein [4]. We have also identified sulfated groups in the N-glycosidic 2

Chains of a T. cruzi glycoprotein with SCP activity. The native SCP co-purifies with Cz from Concanavalin-A affinity columns, the Cz-SCP mixture, purified SCP or Cz were desulfated, ascribing the cross-reactivity between both molecules to the presence of sulfated groups. UV-MALDI-TOFMS confirmed the presence of short-sulfated high-mannose-N-type oligosaccharide chains. Interestingly, we have shown for the first time that SCP is a minor antigen recognized by most of chronic-Chagas-disease-patient´s sera. The involvement of sulfated groups was found in the immune cross-reactivity between Cz and SCP. The MALDI-TOF mass spectra has demonstrated for the firsttime short chain sulfated high mannose type oligossacaridic chains on N-Glycans linked to hexosamines of a T. cruzi SCP [5].

ROLES OF SULFOTOPES

In addition to the humoral immune responses identified towards sulfotopes from sulfated glycoproteins, the synthetic anionic sugar conjugates containing N-acetyl D glucosamine-6-sulfate (NAcGlc6-SO_3) characterized mimics the N-glycan-linked sulfated epitope (sulfotope) exhibited in the C-T domain of Cz [6]. Our findings have established that i) the in vivo effects of sodium chlorate on Cz-sulfation evidenced the participation of sulfotopes in the infection of cardiac cells by trypomastigotes [7]; ii) that Cz sulfated moieties are capable to interact with the immunomodulatory sialic-acid-Ig-like-specific-lectin Siglec-E [8]; and iii) sulfotopes produce muscle tissue injury in BALB/c mice, in absence of infection. It was demonstrated that sulfotopes from Cz and other sulfated glycoproteins take part in parasite infection [7]; immunomodulation [8] and immunopathogenesis [9]. Patients from G0/G1 and G3 groups in accordance to Kurchnir classification, showing differences in degree of cardiac dysfunction (mild vs severe), but no differences were observed in SCP recognition between them. Both presented a significant variable recognition of SCP in comparison with sera from healthy subjects with no recognition [6]. By contrast, the antibodies specific for sulfotopes of Cz and sulfatides (IgG2-$S0_3$) in chronic Chagas disease patients are inversely correlated with the clinical cardiac status of chronic CD [10].

CONCLUSION

Original glycomic mass spectrometry analysis showed the presence of common sulfotopes between both parasite glycoproteins, and the enhanced existence of sulfotopes in trypomastigotes, probably involved in parasite-host relationship and infection. Moreover, that IgG2SO_3 antibody levels specific for sulfotopes showed to be inversely correlated with Chagas disease severity. Ongoing assays will elucidate whether sulfotopes and/or their specific antibodies are responsible for the ultrastructural abnormalities observed in the outcome of the experimental CD disease and potential biomarkers in the progression of human CD severity, respectively. Antibodies specific for sulfotopes might play a role as predictors of stability from the early stages of chronic CD and the analysis of their decrease in levels might be considered as surrogate biomarkers of human CD progression in a near future.

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