ST8Sia2: The host's enchanted armor protecting against T. cruzi infection

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Glycosylation is a highly diverse co- and/or post-translational modification process crucial for the structural and biological functions of a cell. It involves the dynamic addition and removal of sugars, known as glycans, to proteins, lipids, and small RNAs in eukaryotic cells, facilitated by an elegant and sophisticated repertoire of enzymes. Among these modifications, polysialic acid (polySia) stands out due to its unique polymeric structure, formed by the repeated enzymatic addition of sialic acid units by polysialyltransferases such as ST8Sia2. While the importance of polySia in the nervous system is well-documented, its role in host-pathogen interactions remains largely unexplored. Our study reveals the protective role of ST8Sia2-mediated polysialylation in the context of *T. cruzi* infection, the causative agent of Chagas disease, and demonstrates for the first time the interplay between polysialylation and oxidative stress. To unravel the host protective mechanisms mediated by ST8Sia2, we employed a combination of *in silico* and experimental tools to assess host polysialylation levels during *T. cruzi* infection. Our findings indicate that *T. cruzi* infection significantly downregulates ST8Sia2 expression and reduces polysialylation in host cells. Inhibition of ST8Sia2, either genetically or chemically, increases *T. cruzi* load within host cells, suggesting a critical defensive role of polySia against the parasite. Intriguingly, we observed that modulation of polysialylation induces oxidative stress, evidenced by increased reactive oxygen species (ROS) production. This oxidative microenvironment appeared to favor *T. cruzi* survival and replication, indicating a complex interplay between host polysialylation and pathogen evasion mechanisms. Our study highlights ST8Sia2 as a pivotal component of the host defense system,

conferring protection against *T. cruzi* infection. These insights open new avenues for therapeutic interventions aimed at enhancing host polysialylation to strengthen cellular defenses against *T. cruzi* and potentially against other pathogens. Further research into the mechanistic details of ST8Sia2's protective role could pave the way for innovative treatments for Chagas disease.

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