THE IL-33/ST2 AXIS IN *Trypanosoma cruzi* EXPERIMENTAL INFECTION: IMPLICATIONS FOR EARLY MYOCARDITIS AND BEHAVIORAL CHANGES

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Chagas disease (CD), caused by the protozoan *Trypanosoma cruzi*, leads to severe tissue dysfunction, with the host immune response playing a dual role in parasite control and tissue damage. Interleukin-33 (IL-33), an alarmin released upon cellular injury, signals through the ST2 receptor with protective or detrimental effects, but its role in *T. cruzi* infection remains understood. This study aimed to elucidate the impact of IL-33/ST2 signaling on CD pathogenesis. Female BALB/c wild-type (WT) and ST2 knockout ($ST2^{-/-}$) mice were intraperitoneally infected with 1000 *T. cruzi* Y strain trypomastigotes, and parasitological, immunological, and behavioral parameters were assessed. In the acute phase, despite similar parasitemia kinetics, WT infected mice exhibited severe clinical manifestations, including weight loss, reduced food intake and hypothermia. In contrast, $ST2^{-/-}$ infected mice showed an increased leukocyte count, mainly monocytes. Early myocarditis (7 dpi) was observed in $ST2^{-/-}$ mice, characterized by extensive inflammatory infiltrates, whereas WT mice displayed minimal or no cardiac involvement. By 20 dpi, $ST2^{-/-}$ mice developed cardiomyocyte degeneration and fibrosis. In the brain, both infected groups developed multifocal inflammatory foci. However, WT infected mice presented numerous amastigote nests in the cerebral cortex and cerebellum, whereas $ST2^{-/-}$ mice exhibited parasite nests only in the cortex. In the chronic phase (100 dpi), WT mice demonstrated persistent feeding suppression, clinical impairment, and behavioral dysfunction, including anxiety- and depressive-like behaviors. ST2-deficient mice, however, sustained normal feeding behavior and did not develop cognitive defects, suggesting a role of the IL-33/ST2 pathway in behavioural dysfunction during CD. These findings highlight the IL-33/ST2 axis as a critical regulator of immune-mediated pathology in *T. cruzi* infection, with distinct tissue-specific effects across acute and chronic disease phases.

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