XVII INTERNATIONAL SYMPOSIUM ON
SCHISTOSOMIASIS
PERSPECTIVES ON SCHISTOSOMIASIS ELIMINATION
NOVEMBER 10-13TH 2024 | SALVADOR - BAHIA

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TITLE

SEX DIFFERENCES IN PATHOGENIC NEUTROPHIL RESPONSES DURING SCHISTOSOMIASIS

AUTHORS

Souza, C.O.S.*[1]; Borden, O.[1]; Loke, P.[1]

AFFILIATIONS

[1] Type 2 Immunity Section, Laboratory of Parasitic Disease, National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Health (NIH), Bethesda, MD, United States

ABSTRACT

Schistosomiasis is a chronic helminth disease that can progress to severe fibrosis and eventually death in some individuals but not others. This heterogeneity of immune responses and susceptibility to infection is associated with genetic factors. Our results show that male C57BL/6 are more resistant to S. mansoni infection than BALB/c mice. Susceptibility in BALB/c was positively correlated with a pathogenic type 2 immune response driven by neutrophils. In the liver, we observed neutrophilic granulomas with a substantial neutrophil elastase trap (NET) release in BALB/c mice. Additionally, infected BALB/c neutrophils increase reactive oxygen species (ROS) release compared to C57BL/6 neutrophils upon PMA activation. Moreover, ROS inhibition in infected-BALB/c mice reduced ALT levels to baseline levels. In humans, AST levels are positively correlated with neutrophils in patients with severe schistosomiasis. Together, these results suggesting neutrophils drive liver injury during schistosomiasis. However, other intrinsic host factors may also contribute to the severity and pathogenic neutrophil responses during schistosomiasis. Males are more vulnerable to infections and death than females, and sex hormones have been associated with increased neutrophils counts and degranulation. Based on this, we evaluated mortality by genotype and sex. C57BL/6 mice are the most resistant across both sex and genotype, while female BALB/c mice were more resistant than males BALB/c, suggesting that both genotype and sex impact disease severity. Next, we measured ROS release in neutrophils from male and female BALB/c. Upon PMA stimulation, male neutrophils release more ROS than female neutrophils, suggesting that male hormones may affect neutrophil function. To validate the role of male hormones in the neutrophil, we performed castration in male BALB/c mice. Castrated BALB/c mice displayed neutropenia and lymphocytosis in the blood. In the bone marrow (BM), castration did not affect GMP progenitor or pre-neutrophils, but male hormones played a role in the neutrophil maturation. Compared to male BALB/c, immature Ly6G+CXCR2- and mature Ly6G+CXCR2+ neutrophils were reduced in the BM from castrated BALB/c male. Together, these results suggest that male hormones contribute to pathogenic neutrophil responses during schistosomiasis.

KEYWORDS

Schistosomiasis; Neutrophil; Pathogenic; Sex hormones

FINANCIAL SUPPORT