Inhibition of PGD_2 synthesis or DP2 receptors activation aggravates *Schistosoma mansoni* infection-induced hepatic granulomatous fibrosis

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Introduction

During the defensive immune response to *Schistosoma mansoni* infection, numerous and long-lasting egg-encasing hepatic granulomas display severe fibrosis which promotes schistosomiasis-related clinical morbidity and mortality. Therefore, identification of molecules capable of controlling the fibrotic process within *S. mansoni* induced hepatic granulomas is germane. The immunomodulatory lipid PGD_2, known to be synthesized by both *S. mansoni* itself and host cells, has recently been proposed as a promising target for anti-fibrotic therapeutic intervention in schistosomiasis. Here, we investigated the role of host-derived PGD_2 and the activation of DP2 receptors in schistosomiasis-related hepatic granulomatous fibrosis.

Methods

We used two pharmacological strategies, the specific inhibitor of host hematopoietic PGD synthase HQL-79 or the DP2 receptor antagonist CAY10471. Male C57BL/6 mice were infected with 60 *S. mansoni* cercariae. At 24^{th} day of infection, osmotic pumps (Alzet® pump; flow rate 0.11 µL/hour)–containing 100 µL of either HQL-79 (1 mg/mL) or CAY10471 (670 µg/mL) solutions and pumping about 2.6 or 1.7 µg/day, respectively–were implanted subcutaneously. Blood and feces were collected at 0th, 15th, 30th, 45th and 55th days of infection. At this point, mice were euthanized for analysis of parasitemia, systemic eosinophilia and hepatic granulomatous fibrosis (all protocols were approved by the Committee for Ethics in Animal Experimentation (CEUA 115/14 CCS) at UFRJ.

Results

The treatment with HQL-79 reduced *S. mansoni* egg occurrence in hepatic and intestinal sites, decreased blood eosinophilia and eosinophil migration from peripheral blood to peritoneal cavity and hepatic granulomas of the infected mice, while the CAY10471 treatment did not affect the egg occurrence in both sites, but decreased the eosinophilia in the bone marrow and peritoneal cavity without affecting it in the peripheral blood. Both treatments promoted amplification of fibrotic response within schistosomal hepatic granulomas characterized by increased hepatic levels of collagen fibers, IL-13 and TGFβ.

Conclusion

Together, the results disclose differences between losing both DP1 and DP2 receptors activation *versus* only blocking the DP2 receptor, suggesting that these receptors act together in a combined manner during infection. Our findings unveil an essential role for this prostanoid in inducing the classical schistosomiasis eosinophilia and suggest that the DP1 receptor may display an important and complementary role. More importantly, even though early studies have postulated PGD_2 as a pro-fibrogenic molecule, data presented here shows that, endogenous PGD_2 acting on DP2 receptors attenuates fibrosis of hepatic granulomas, therefore, indicating that therapeutic strategies targeting PGD_2/DP2 axis during schistosomal infection should be avoided. Studies investigating the role of DP1 receptor activation on hepatic granulomatous fibrosis are ongoing.

Financial support : CAPES,CNPQ,FAPERJ
Keywords: PGD_2;Schistosoma mansoni;Eosinophil;DP2;fibrosis