Skin Reactivity to Aeroallergens in *Schistosoma mansoni*–Infected Brazilian Individuals and Modulation of CCL2 and IL-10

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Infection with *Schistosoma mansoni* triggers immunoregulatory mechanisms, which suppress the positivity of immediate hypersensitivity reactions [1]. Chemokines influence cellular traffic [2], although there are few studies about the relationship between chemokines, cutaneous reactivity, and infection by *S mansoni*. This study investigated levels of CCL2, CCL5, CXCL8, CXCL9, and CXCL10 from individuals with schistosomiasis, as well as the frequency of positive skin prick test (SPT) results with aeroallergens.

The patients involved in the study provided their informed consent, and 118 individuals from urban areas (Cabo de Santo Agostinho and Itamaracá Island, Pernambuco, Brazil) were classed as being infected by *S mansoni* (Sm+) or not infected (Sm–) according to the Kato-Katz and Hoffman-Pons-Janer methods. A positive SPT result was defined as a reaction (50 000 SBU/mL, IPI-ASAC) to at least 1 allergen (*Dermatophagoides pteronyssinus, Blomia tropicalis, Periplaneta americana, Blattella germanica, Felis domesticus, Aspergillus fumigatus, Penicillium notatum*, and *Alternaria alternata*). Histamine (10 mg/mL) was used as a positive control, and positive reactions were defined as wheal diameters at least 3 mm larger than the negative control (saline) after 20 minutes. We formed 4 groups: SPT+/*Sm*+; SPT+/*Sm*–; SPT–/*Sm*+; SPT–/*Sm*–. A socioeconomic questionnaire and the questionnaire of the International Study of Asthma and Allergies in Childhood (ISAAC) were completed [3,4]. The information collected from the ISAAC questionnaire was the number of asthma attacks in the previous year, sleep disturbance due to attacks, difficulty speaking during attacks, wheezing after exercise, and dry cough at night. The variables related to allergic rhinitis were sneezing accompanied by tearing and the extent to which this disrupted the patient's life.

Peripheral blood was cultured with a mitogen (10 µg/mL of phytohemagglutinin for 24 hours at 37°C in 5% CO_2), and the supernatants were evaluated for the presence of chemokines using a cytometric bead array on a flow cytometer (FACSCalibur, BD Biosciences). The procedure was performed according to the instructions of the manufacturer of the Human Chemokine Kit (Cat. No. 552990). BD CellQuest software was used for sample acquisition, and FCAP software (version 3.01) was used for data analysis. IL-10 (Human IL-10 Flex CBA, Cat. No 558274), total IgE, and the most common allergen in the local study (anti–*Blomia tropicalis* IgE) [5] were measured using fluoroimmunoassay (ImmunoCAP-Phadia).

The results were presented as the median (IQR). The χ^2 and Fisher exact tests were used to compare the frequencies of SPT positivity; the Kruskal-Wallis and Mann-Whitney tests were used to compare chemokine, IL-10, and IgE levels. The study was approved by the Committee of Ethics in Research of the Aggeu Magalhães Institute/Fiocruz (CAAE: 22822813.3.0000.5190).

Of the 118 selected individuals, 54 were infected (45.8%) (median parasite load, 24 [24-48] eggs/g), including 24 males (44.4%). Median age was 27 (19-42.5) years. Of the 64 noninfected patients (54.2%), 26 were males (40.6%). Median age was 36.5 (11-47) years. There were no differences in age or sex between the groups. After a logistic multivariate analysis adjusted for age and sex, there was no association with allergy in relatives, maternal educational status, and smoking.

Consistent with polyclonal activation in helminthiasis, median total IgE levels were higher in SPT+/Sm+ (1125 [134.57-2945.75] kU/L) and SPT–/*Sm*+ (712 [280.5-2481] kU/L) than in SPT–/Sm– (177 [47.7-1126] kU/L) (*P*=.030). Anti–*B tropicalis* IgE levels were higher in SPT+/*Sm*– (1.29 [0.002-8.52] kU/L) than in SPT+/Sm+ (0.93 [0.14-1.702] kU/L), SPT–/*Sm*+ (0.14 [0.08-1.17] kU/L), and SPT–/*Sm*– (0.19 [0.01-3.3] kU/L) (*P*=.039). The frequency of cutaneous reactivity to the aeroallergens was lower for infected individuals than for the noninfected group (OR, 0.351; 95%CI, 0.153-0.802; *P*=.017). Of the Sm+ individuals, 20.37% (11/54) had positive SPT results to aeroallergens and 79.63% (43/54) had negative results. Among Sm– individuals, 42.19% (27/64) reacted to the SPT, whereas 57.81% (37/64) did not.

Of the 118 individuals, 38 were allergic (asthma, 14; rhinitis, 8; asthma and rhinitis, 16) (32.20%). Among allergic individuals, 10 (26.31%) were infected and 28 (73.68%) were not (OR, 0.29; 95%CI, 0.12-0.68; *P*=.003). With respect to symptoms, 16 of the 38 of allergic individuals (42.1%) had dry cough at night: 1 (6.25%) was infected, whereas 15 (93.75%) were not. Sleep was disturbed by the asthma attacks in 10 of the 38 allergic individuals (26.31%), of whom 1 (10%) was infected and 9 (90%) were not. Difficulty speaking during the attacks was recorded in 8 of the 38 patients (21.05%), of whom 1 (12.5%) was infected and 7 (87.5%) were not. Sneezing accompanied by tearing affected 14 of the 38 patients

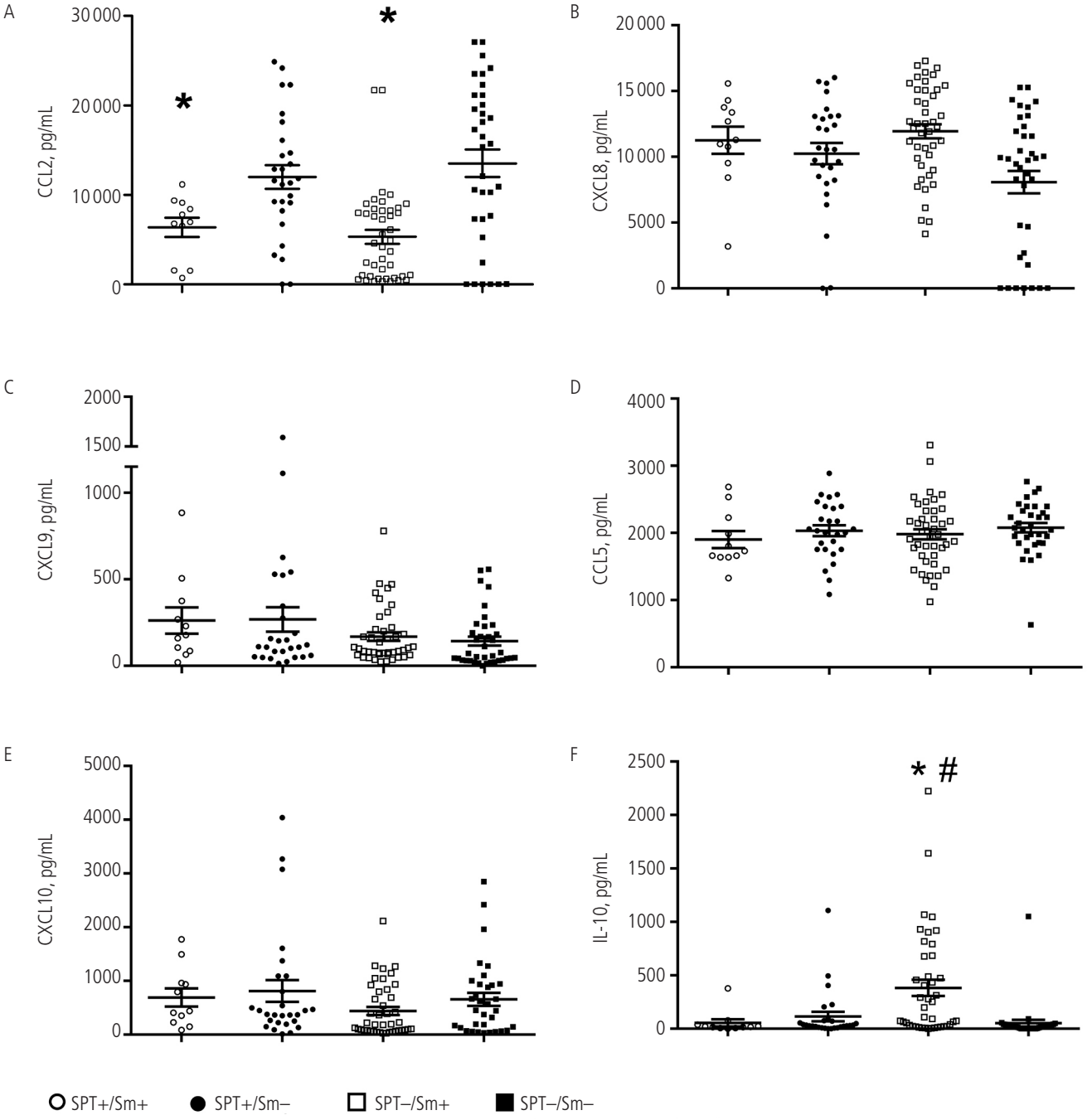

Figure. Levels of the chemokines CCL2 (A), CXCL8 (B), CXCL9 (C), CCL5 (D), and CXCL10 (E) and the cytokine IL-10 (F) measured in 24-hour peripheral total blood culture supernatants, which were stimulated with phytohemagglutinin, in SPT-positive individuals infected by *Schistosoma mansoni* (SPT+/*Sm*+) (n=11), SPT-positive and noninfected patients (SPT+/*Sm*–) (n=27), SPT-negative patients infected by *S mansoni* (SPT–/*Sm*+) (n=43), and SPT-negative noninfected patients (SPT–/*Sm*–) (n=37). The Kruskal-Wallis test was performed to compare the medians between the groups. **P*<.05 compared with the SPT+/*Sm*– and SPT–/*Sm*– groups. #*P*<.05 compared with the SPT+/*Sm*+.

(36.84%), 5 (35.71%) of whom were infected and 9 (64.29%) were not.

The levels of CCL2 in the SPT+/Sm+ and SPT–/Sm+ groups were lower than those in the SPT+/Sm– and SPT–/Sm– groups (Figure, A). There were no differences between the groups in production of CXCL8, CXCL9, CCL5, and CXCL10 (Figure, B-E). IL-10 production was higher in SPT–/Sm+ than in SPT+/Sm+ and SPT–/Sm– (Figure, F).

The results of this study are similar to those of other authors [1]: infection by *S mansoni* had a negative effect on the SPT result, asthma symptoms, and IgE levels and elicited production of IL-10. For the first time, an inverse association was demonstrated between *S mansoni* infection and CCL2 levels.

CCL2 can significantly affect the allergic response owing to its capacity to attract eosinophils and activate mastocytes/basophils [2,6]. In this way, CCL2 can stimulate the release of histamine and leukotrienes [6-8]. Therefore, the lowest sensitivity of SPT in the infected group can reflect a less marked effect of CCL2 on mastocytes. We also highlight the higher production of IL-10 in infected individuals, suggesting that inflammation is inhibited by this cytokine during the immediate cutaneous hypersensitivity reaction [1,9]. In fact, IL-10 is associated with a negative effect on the synthesis of chemokines [2], including CCL2 [10].

We are aware that production of CCL2 was measured in blood samples and may not therefore be representative of the local reaction. Consequently, the results highlight the need to study the role of *S mansoni* molecules in therapy and that of CCL2 production as a target in skin reactions. In conclusion, the data suggest that the influence of IL-10 may reduce the likelihood of immediate cutaneous hypersensitivity in individuals with schistosomiasis, which in turn could play a role in the production of CCL2.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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