Published in final edited form as:
J Infect Dis. 2009 January 15; 199(2): 272–279. doi:10.1086/595792.

Circulating CD23+ B Cell Subset Correlates with the Development of Resistance to *Schistosoma mansoni* Reinfection in Occupationally Exposed Adults Who Have Undergone Multiple Treatments

Pauline N. M. Mwinzi[1,a], **Lisa Ganley-Leal**[2,a], **Carla L. Black**[3], **W. Evan Secor**[4], **Diana M. S. Karanja**[1], and **Daniel G. Colley**[3]

1*Center for Global Health Research, Kenya Medical Research Institute, Kisumu, Kenya*

2*Section of Infectious Diseases, Department of Medicine, Boston University School of Medicine, Boston Medical Center, Boston, Massachusetts*

3*Center for Tropical and Emerging Global Diseases and Department of Microbiology, University of Georgia, Athens*

4*Division of Parasitic Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia*

Abstract

Background—Elevated immunoglobulin E (IgE) levels are often associated with resistance to reinfection in human schistosomiasis. However, Although B cells are the source of schistosome-specific IgE, little is known about B cell subsets or their functions in this infection. We evaluated B cells and their expression of the low-affinity IgE receptor (CD23) in a unique cohort of men occupationally exposed to *Schistosoma mansoni* and longitudinally followed up through multiple treatments with praziquantel, cures, and reinfections.

Methods—Resistance levels were calculated on the basis of documented water exposure and reinfection data over many years. The $CD23^+$ B cell subset was evaluated in whole blood by flow cytometry. Serum antibody isotype and soluble CD23 (sCD23) concentrations were measured by enzyme-linked immunosorbent assay.

Results—Expression of membrane CD23 (mCD23) on B cells correlated with the development of resistance against *S. mansoni*. Higher levels of plasma sCD23, the cleaved form of mCD23, also correlated with resistance and other markers of resistance to reinfection, such as eosinophilia.

Conclusions—CD23 may be involved in the development of resistance to schistosome infection through its role in IgE regulation. Understanding these complex host-parasite interactions may lead to insights into the development, mechanisms, and regulation of resistance to reinfection with *S. mansoni*.

Infection with *Schistosoma mansoni* remains a major public health problem in many resource-limited countries in the world. There are costs and logistical challenges associated with

Reprints or correspondence. Dr. Daniel Colley, Center for Tropical and Emerging Global Diseases, Coverdell Center, Rm. 330B, University of Georgia, 500 D. W. Brooks Dr., Athens, GA 30602−3799 (dcolley@uga.edu)..

[a]P.N.M.M. and L.G.-L. contributed equally to this work.

Potential conflicts of interest: none reported.

Presented in part: 56th Annual Meeting of the American Society for Tropical Medicine and Hygiene, Philadelphia, 4−8 November 2007 (abstract 664).

chemotherapy and sanitation-based control, and a vaccine might be needed as an additional tool for long-term control or elimination [1]. However, vaccine development has been hindered by limited translational data from studies in laboratory animals and an inadequate understanding of the protective immune mechanisms in humans [2]. Recent data showing that a proportion of adults occupationally exposed to *S. mansoni* can become more resistant to reinfection [3] have encouraged continued research into a vaccine. Studies in the human host to further characterize the immune responses that correlate with protection should help in vaccine development.

In many field-based studies, high levels of parasite-specific IgE correlate with resistance in schistosomiasis [4-6], yet our understanding of the mechanisms of IgE regulation is limited. Remarkably, although B cells are the producers of IgE, little is known about human B cell function in schistosomiasis. In mice, B cells have been shown to play an important role in antiparasite immunity, not only as antibody producers but also in promoting an optimal and sustained T cell response [7]. It remains important to define the roles that human B cells play in immunity to schistosomiasis.

IgE most likely exerts in vivo effector and regulatory function(s) through its high-affinity (FcεRI) and/or low-affinity (FcεRII or CD23) receptors on myeloid cells [8]. CD23 is also expressed by B cells. In some settings, CD23-bound IgE cross-linked by antigen activates B cells, and it has been shown to regulate IgE production. However, although CD23 may exercise opposing roles in IgE immune responses in mice [8,9], it appears to be a positive regulator in humans and may have an important role in human immunology [10]. IgE-antigen complexes also enhance human B cell antigen presentation to T cells in vitro, although the specific intracellular mechanisms have not been detailed [9,11,12]. Thus, the production and regulation of IgE may be mediated in part through $CD23^+$ B cells [8,12-17]. The mechanisms of high IgE output at the level of the B cell are not well characterized in schistosomiasis, and it is not understood why some individuals develop high IgE levels and others do not, despite generally comparable levels of exposure. We have studied CD23 expression on B cells in a unique setting involving the development of demonstrable resistance to natural reinfection by *S. mansoni* in humans. We show that levels of both $CD19^+CD23^+$ B cells and circulating soluble CD23 (sCD23) correlate with the development of resistance to reinfection and with other indicators of resistance, such as eosinophilia, during a defined period of multiple praziquantel treatments and reinfections.

METHODS

Study participants

This study was conducted from 1995 to 2007 in Kisumu in western Kenya, on the shores of Lake Victoria. Transmission along the lake shore has been confirmed by the identification of *S. mansoni*–infected *Biomphalaria sudanica* snails (authors' unpublished data) at the exposure site. The study participants were men employed as car washers and thus occupationally exposed to schistosome transmission as they washed cars while standing in the lake, as described elsewhere [3]. Water-contact data were obtained by recording the number of cars washed daily by each man. Study participants were also characterized by their duration of follow-up and numbers of treatments and cure episodes. Adult car washers who had been followed up for up to 12 years were included in the present investigation. Participants were grouped for analyses on the basis of the number of years they had participated in this longitudinal study: <3, 3− 6, and >6 years. Initial analyses of $CD23^+$ B cell populations over the entire follow-up period did not yield meaningful correlations. However, stratification on the basis of these periods of follow-up provides insights into relationships between the development of resistance and several immune parameters.

After informed consent was obtained from subjects and their participation in HIV counseling and testing was confirmed through the Kenyan Ministry of Health Volunteer Counseling and Testing Service, independent HIV-1 screening was done (Determine HIV-1/2; Abbott), and confirmatory tests were performed on positive samples (Uni-Gold; Trinity Biotech). This investigation was approved by the institutional review boards of the University of Georgia and the Centers for Diseases Control and Prevention, the Scientific Steering Committee of the Kenya Medical Research Institute, and the National Ethics Review Board of Kenya. Stool samples were examined for *S. mansoni* eggs and for other helminth ova by the modified Kato-Katz method (Vestergaard Frandsen) (2 slides each, 3 stool specimens obtained over several days). Subjects positive for *S. mansoni* were treated with 40 mg/kg praziquantel; those positive for other helminth ova were treated with 400 mg of albendazole. $CD4^+$ and $CD8^+$ cell counts and whole-blood differentials were determined by FACSCount and Coulter counter analysis, as reported elsewhere [18-20].

Cell-surface staining and flow cytometry analysis

Blood was collected by venipuncture into EDTA-coated glass tubes (BD Vacutainer System). To identify membrane CD23 (mCD23) on peripheral blood B cells, anti-CD19, anti-CD23 (e-Bioscience), and anti-IgM (Southern Biotech) were used. Gating to separate $CD23^-$ from $CD23^+$ B cells was based on fluorescence minus one (FMO)– stained samples (figure 1). To examine phenotypic subsets of $CD19^+CD23^+$ B cells, the following antibodies were used: anti-CD27 (e-Bioscience), anti-IgM (Southern Biotech), and anti-IgE (BD Pharmingen). Isotype controls or FMO-stained samples were used to separate positive from negative subsets (figure 1).

ELISA

The sCD23 ELISAs were performed according to the manufacturer's recommendation (Bender MedSystems). Anti–soluble worm antigenic preparation (SWAP) IgE isotype assays were performed using standardized ELISA methods, as described elsewhere [21].

Determination of relative resistance or susceptibility to reinfection after cure

The index of susceptibility/resistance (IoS/R) was defined as follows: (number of reinfections/total number of cars washed in intervals between cure and reinfection) × 100. Documented cure was defined as negative results for *S. mansoni* eggs in 3 consecutive stool samples (2 slides each), according to the Kato-Katz technique. The criterion for reinfection after documented cure was positive results for *S. mansoni* eggs, as determined by sampling stool longitudinally every 4 weeks. If the subject was negative for eggs in the stool when blood was sampled, his IoS/R was calculated up to and including the date of his next reinfection after the date of blood sampling. If the subject was positive for eggs in the stool at the time of blood sampling, his IoS/R was calculated using the last reinfection date before the blood sampling date. Excluded from the calculation of IoS/R were the numbers of cars washed during cure and reinfection intervals that spanned >3 years or >3 reinfections before the blood sampling date under study. Therefore, for those with >3 previous cures, only the number of cars washed during the last 3 intervals are included in the denominator of the IoS/R calculation. This method generates index values comparable to our previous data [3,19,20] but has been revised to represent a subject's resistance status during a reasonably discrete period of time before the blood sampling date rather than over the entire course of their follow-up. For newly enrolled car washers who had not experienced a cure before the date of blood sampling, the IoS/R was based on the number of cars washed during the interval between the first cure after the blood sampling date and the first subsequent reinfection. In our analyses, to determine resistance status judiciously, we excluded 8 observations owing to inadequate follow-up around the time the blood samples were obtained.

Statistical analyses

Statistical analyses were performed using GraphPad Prism (version 4.0 for Windows; GraphPad Software) and Microsoft Excel software. One-way analysis of analysis of variance with Dunn's posttest and the Mann-Whitney *U* test were used for multiple- or single-group comparisons, respectively. Possible correlations between $CD19^+CD23^+$ percentages or levels of sCD23 and IoS/R or eosinophils were examined using Spearman's rank correlation test. Differences were considered statistically significant at $P < .05$. Group sample sizes differ among the tests because some patient samples were unavailable.

RESULTS

B cell subsets and sCD23 levels in plasma were evaluated in venous blood samples provided by 20 men (19 HIV negative and 1 HIV positive) followed up for <3 years, 37 men (20 HIV negative and 17 HIV positive) followed up for 3− 6 years, and 21 men (11 HIV negative and 10 HIV positive) followed up for >6 years. Because of multiple sampling in some participants, 4 men are represented in both the <3-year and 3− 6-year follow-up categories, and 12 men are represented in both the 3− 6-year and >6-year categories. As expected, the $CD4^+$ cell counts (mean ± SD, 526 ± 279 vs. 803 ± 307 cells/μL) were lower ($P = .002$) and the $CD8^+$ cell counts (1053 ± 582 vs. 531 ± 254 cells/μL) were higher ($P < .001$) in *S. mansoni*–infected donors coinfected with HIV-1 than in those without HIV-1 coinfection. However, all but 1 of the HIV-1–seropositive subjects had $CD4^+$ cell counts >200 cells/μL. The mean percentage of circulating $CD19^+$ B cells was significantly higher among HIV-1–negative than HIV-1–positive participants (mean ± SD, 10.6% ± 4.4% vs. 7.1% ± 2.7%) ($P = .016$).

$CD23^+$ B cells in human schistosomiasis

The expression of mCD23 on circulating $CD19^+$ B cells was evaluated ex vivo in fresh whole-blood samples by flow cytometry, using the gating strategy shown in figure 1. The mean ± SD level of $CD19^+CD23^+$ cells (i.e., $CD23^+$ B cells) in the entire cohort was 55.9% ± 21.1%, and this percentage was positively related to the level of CD23 surface expression on $CD19^+$ cells, as measured by mean fluorescence intensity ($r = 0.5672$; $P < .001$). Within the limits of detection, all $CD23^+$ cells in the lymphocyte gate were $CD19^+$ (figure 1), and 98.6% of these $CD23^+$ B cells were IgM^+ (figure 1). A small percentage of $CD23^+$ B cells also coexpressed CD27 (mean ± SD, 11.8% ± 6.7%; range, 1.4%−28.4%), a marker for memory lymphocytes, suggesting that a subpopulation of $CD23^+IgM^+CD27^+$ B cells may originate from the splenic marginal zone (figure 1) [22]. Because CD23 is an IgE receptor, we examined whether some circulating $CD23^+IgM^+$ B cells also bound to IgE. Indeed, IgE could be detected on the surface of some $CD23^+$ B cells, indicating that these B cells can circulate with IgE preloaded on their surface (figure 1).

Association between $CD23^+$ B cell and sCD23 level and resistance to S. mansoni reinfection in persons undergoing multiple treatments and reinfections

To determine whether levels of $CD23^+$ B cells were related to resistance, subjects' individual percentages of $CD23^+$ B cells were plotted against their IoS/R values at the time of sampling. Among subjects who had been undergoing repeated treatments and reinfections for 3− 6 years, there was a positive correlation between $CD23^+$ B cell levels and increased resistance to schistosome reinfections (lower IoS/R values) ($r = −0.5203$; $P = .019$) (figure 2*a*), regardless of HIV-1 serostatus. This relationship did not hold for those followed up for >6 years ($P = .168$) (figure 2*b*)or <3 years ($P = .242$) (figure 2*c*).

mCD23 can be cleaved from cell surfaces by endogenous proteases and can be measured in the plasma in a soluble form (sCD23) [14,15]. We analyzed sCD23 values in relation to IoS/R values and saw a significant correlation for the group followed up for 3− 6 years ($r = −0.4176$;

P = .027) (figure 3*a*), if we excluded 1 observation for which both values were well out of the range of other observations (sCD23 level, 34.8 U/mL; IoS/R value, 0.7444). There was no correlation between sCD23 levels and IoS/R values in those followed up for >6 years (P = .766) (figure 3*b*)or <3 years (P = .342) (figure 3*c*). As with mCD23, the HIV-1 serostatus of an individual did not affect these relationships between CD23 expression and resistance to reinfection (figure 3).

Relationship between sCD23 levels and eosinophilia, an other marker of resistance

In another study, we confirmed that eosinophilia is associated with resistance to reinfection [20]. There was a positive relationship between the percentages of circulating $CD23^+$ B cells and eosinophils among those in the 3− 6-year follow-up group, but it was not statistically significant (P = .198; data not shown). Likewise, when the relationship between circulating sCD23 levels and eosinophils was examined for all subjects (HIV-1 seropositive and seronegative), no significant correlation was observed in the 3− 6-year follow-up group (figure 4*a*). However, when only the HIV-1–seronegative subjects in this group were analyzed, there was a significant positive correlation between circulating sCD23 levels and eosinophilia (figure 4*b*)(r = 0.6711; P = .004). This relationship did not hold for those followed up for >6 years (P = .872) or <3 years (P = .770). That HIV-1 serostatus affected the relationship between sCD23 and eosinophilia was not unexpected, because we have reported previously that eosinophilia (a correlate of the level of resistance) was related to $CD4^+$ cell count in this population [20]. We also found a relationship between the level of mCD23 expression on B cells (measured by mean fluorescence intensity) and circulating anti-SWAP IgE levels by linear regression analysis of the 3− 6-year follow-up group (r = 0.395; P = .038), but these parameters were not significantly correlated by Spearman's rank correlation test (r = 0.382; P = .248), possibly because we had complete data for only 11 individuals (data not shown).

Other observations based on stratification into follow-up groups

Examination of our cohort stratified according to the duration of longitudinal follow-up provided confirmation of earlier findings [3] and insights into what occurs during periods of repeated treatment and reinfection. As expected, longer follow-up times led to more treatment (figure 5*a*), which could result from either reinfection or failure to cure. Consistent with our previous findings [3], we observed that longer follow-up and increased numbers of treatments led to decreased mean IoS/R values (greater relative resistance) in the 3− 6-year follow-up group compared with the <3-year follow-up group (figure 5*b*). Furthermore, although mean anti-SWAP IgE levels did not differ significantly (P = .088), there was a significant trend (P = .032) toward higher levels of SWAP-specific IgE with longer follow-up, increased repeated treatments, and lower IoS/R values (figure 5*c*).

DISCUSSION

Acquired resistance to *S. mansoni* reinfection is well documented [23,24], and we have reported previously that repeated treatments and reinfections can lead to higher levels of resistance [3]. However, the mechanisms of resistance remain poorly understood. IgE is found in nanogram amounts in human serum [15], but relatively high levels are reported in persons with helminth infections. Several field-based studies have found a consistent correlation between resistance to reinfection and these high levels of IgE [4-6]. Yet it remains unknown whether anti-schistosome IgE is directly involved in protection—and, if so, how. Nevertheless, B cells produce IgE, so understanding their biology will be critical to understanding the mechanism (s) of regulating anti-schistosome IgE production in this situation of chronic antigen exposure. In fact, the roles proposed for IgE in helminth infections are as diverse as direct killing of worms and regulation of immunity [25,26]. Consistent with findings reported by others, we recently reported that eosinophilia strongly correlates with the ability to resist infection with

schistosomes after praziquantel treatment [20] and, furthermore, that these eosinophils express the FcεRI*β* chain, a molecule that is important in IgE-mediated immunity. Here, we provide evidence that CD23, the low-affinity IgE receptor (FcεRII), is another cell-surface molecule, related, in this case, to the development of enhanced resistance to reinfection with schistosomes.

Cycles of infection, cure, and reinfection contribute to the development of resistance in our cohort, suggesting that praziquantel treatment can augment protective immunity [3]. Our present investigation continues a longitudinal study of men who wash cars in Lake Victoria, and we have grouped these men on the basis of the length of their follow-up times: <3 years, 3− 6 years, or >6 years. Those in the early stage of follow-up (<3 years) experienced, as expected, fewer rounds of treatment (figure 5*a*) and exhibited lower levels of resistance (higher IoS/R values) (figure 5*b*) than the other groups, who were followed up longer and treated more times (figure 5*a* and 5*b*). With a progression to longer follow-up times, there was also a trend toward higher levels of circulating anti-SWAP IgE (figure 5*c*). Our inference from these data is that most men in the <3-year follow-up group have not developed this induced resistance because they have not yet undergone multiple treatments; meanwhile, higher levels of relative resistance are developing in many in the 3−6-year follow-up group and have already been induced in most in the >6-year follow-up group (which still includes some “susceptible” individuals) because of their repeated treatments and reinfections.

We found that in the 3−6-year follow-up group (those actively acquiring increased resistance), both the percentages of $mCD23^+$ B cells and the levels of circulating sCD23 directly correlated with subjects’ relative levels of resistance (IoS/R values) (figures 2*a* and 3*a*). In the group not exposed multiple times to dying worms and whose resistance was, thus, not increased, these correlations were not yet observed, and they were no longer observed in the group with more established resistance (figures 2*b*, 2*c*, 3*b*, and 3*c*). These results suggest that B cell– related CD23 may play a critical role in the development of increased protective immunity. In this group, we also found circulating sCD23 levels to be correlated with peripheral blood eosinophilia; as noted previously [20], this relationship with eosinophilia was seen only in HIV-1–seronegative subjects (figure 4*b*). Moreover, although the correlation was not significant, there was a linear relationship in this group between levels of mCD23 expression on B cells and levels of anti-SWAP IgE. In other situations, CD23 expression on B cells is linked to both positive and negative immune regulation [8, 9], and its expression in this setting of developing resistance may indicate that it is functionally relevant in the active process of increased resistance related to multiple treatments and reinfections. Furthermore, we conjecture that this may also be true in those who develop resistance to reinfection in response to naturally occurring worm death during chronic infection [27].

The expression of CD23 on B cells is increased as they pass from a resting to an activated phase [28] and is higher in persons with asthma or atopy and in disorders characterized by chronic inflammation [29-31]. CD23 has a broad cellular distribution in humans, and its role in immune responses appears highly complex. Its multiple functions are mediated through a range of different ligands, which can bind both mCD23 and sCD23. These include IgE (both in its secreted form and on membranes of class-switched ε B cells), CD21 (complement receptor 2), CD18/ CD11b and CD18/CD11c (complement receptors 3 and 4, respectively), and the vitronectin receptor [32-34]. IgE-coupled activation of CD23 has been shown to contribute to the up-regulation of human IgE production [35], although this can down-regulate mouse IgE synthesis [36]. Participation in human IgE production is thought to occur by internalization of IgE bound to antigen, which augments antigen presentation [35]. Furthermore, some anti-CD23 antibodies decrease human IgE production [34]. Both interleukin (IL)– 4 and IL-13 are strong inducers of CD23 surface expression on human B cells [37,38], and the ability to produce IL-4 in response to schistosome antigens after praziquantel

treatment has been associated with resistance to reinfection [39]. IL-4 probably plays a role in IgE production and eosinophilia, and the observed increased resistance could, in part, be mediated by IL-4.

sCD23 results from cleavage of the 45-kDa mCD23 on B cells and other cells, such as eosinophils [40]. Endogenous proteases cleave the cell-surface protein near the base of its leucine zipper stalk to release a 37-kDa molecule, and at sites closer to the head-lectin region and within the C-terminal tail, resulting in several different-sized sCD23 fragments [41,42]. Because the function of sCD23 on subsequent IgE synthesis depends on whether sCD23 is an oligomer, whether it is a large or small fragment, and to which ligands it binds (CD23-bound IgE, BCRε, CD21) [43], it is important to characterize sCD23 in schistosomiasis.

Our data demonstrate the presence of $CD23^+$ B cells and sCD23 during schistosomiasis and show that their levels are correlated with the active development of resistance in a unique, well-defined cohort for which we have longitudinal data regarding this process. In addition, we noted that some circulating IgM^+CD23^+ B cells are preloaded with IgE, which could contribute to augmented levels of IgE production through cross-linking of CD23-bound parasite-specific IgE with parasite antigen [44]. Given these observations, coupled with the mCD23- and sCD23-related findings in other systems cited above, the role played by $CD23^+$ B cells and sCD23 functions in human schistosomiasis need to be defined more completely through mechanistic, field-based laboratory studies in a variety of immunoepidemiologic situations.

Acknowledgments

We thank Eunice Mailu, Jennifer Carter, Esther Wanjala, Eric Mouk, Erick Livaha, Keziah Odhiambo, YanMei Liang, Daniel Onguru, and Hassan Jimale for technical assistance. We are grateful to all the study participants for their participation.

Financial support: National Institute of Allergy and Infectious Diseases (Public Health Service [PHS] grants AI 053695 to D.G.C., T32 AI060546 to C.L.B., and R21AI074843 to L.G.-L.) and Fogarty International Center (PHS grant D43 TW007123 to P.N.M.M.), National Institutes of Health; Wellcome Trust (grant 083607 to P.N.M.M.); Centers for Disease Control and Prevention; Kenya Medical Research Institute; Evans Medical Foundation, Boston Medical Center.

References

1. Bergquist NR, Leonardo LR, Mitchell GF. Vaccine-linked chemotherapy: can schistosomiasis control benefit from an integrated approach? Trends Parasitol 2005;21:112–7. [PubMed: 15734657]
2. Todd CW, Colley DG. Practical and ethical issues in the development of a vaccine against schistosomiasis mansoni. Am J Trop Med Hyg 2002;66:348–58. [PubMed: 12164288]
3. Karanja DM, Hightower AW, Colley DG, et al. Resistance to reinfection with *Schistosoma mansoni* in occupationally exposed adults and effect of HIV-1 co-infection on susceptibility to schistosomiasis: a longitudinal study. Lancet 2002;360:592–6. [PubMed: 12241930]
4. Dunne DW, Butterworth AE, Fulford AJ, Ouma JH, Sturrock RF. Human IgE responses to *Schistosoma mansoni* and resistance to reinfection. Mem Inst Oswaldo Cruz 1992;87:99–103. [PubMed: 1343933]
5. Rihet P, Demeure CE, Bourgois A, Prata A, Dessein AJ. Evidence for an association between human resistance to *Schistosoma mansoni* and high anti-larval IgE levels. Eur J Immunol 1991;21:2679–86. [PubMed: 1936116]
6. Zhang Z, Wu H, Chen S, et al. Association between IgE antibody against soluble egg antigen and resistance to reinfection with *Schistosoma japonicum*. Trans R Soc Trop Med Hyg 1997;91:606–8. [PubMed: 9463682]
7. Hernandez HJ, Wang Y, Stadecker MJ. In infection with *Schistosoma mansoni*, B cells are required for T helper type 2 cell responses but not for granuloma formation. J Immunol 1997;158:4832–7. [PubMed: 9144498]

8. Gould, HJ.; Beavil, RL.; Reljic, RJ., et al. IgE homeostasis: is CD23 the safety switch?. In: Vercelli, D., editor. IgE regulation: molecular mechanisms. John Wiley & Sons; New York: 1997. p. 35-59.
9. Squire CM, Studer EJ, Lees A, Finkelman FD, Conrad DH. Antigen presentation is enhanced by targeting antigen to the Fc epsilon RII by antigen-anti-Fc epsilon RII conjugates. J Immunol 1994;152:4388–96. [PubMed: 7512593]
10. Mayer RJ, Bolognese BJ, Al-Mahdi N, et al. Inhibition of CD23 processing correlates with inhibition of IL-4-stimulated IgE production in human PBL and hu-PBL-reconstituted SCID mice. Clin Exp Allergy 2000;30:719–27. [PubMed: 10792365]
11. Westman S, Gustavsson S, Heyman B. Early expansion of secondary B cells after primary immunization with antigen complexed with IgE. Scand J Immunol 1997;46:10–5. [PubMed: 9246203]
12. Getahun A, Hjelm F, Heyman B. IgE enhances antibody and T cell responses in vivo via $CD23^{+}$ B cells. J Immunol 2005;175:1473–82. [PubMed: 16034084]
13. Matz J, Williams J, Rosenwasser L, Borish L. Granulocyte-macrophage colony-stimulating factor stimulates macrophages to respond to IgE via the low affinity IgE receptor (CD23). J Allergy Clin Immunol 1994;93:650–7. [PubMed: 8151065]
14. Pongratz G, McAlees JW, Conrad DH, Erbe RS, Haas KM, Sanders VM. The level of IgE produced by a B cell is regulated by norepinephrine in a p38 MAPK- and CD23-dependent manner. J Immunol 2006;177:2926–38. [PubMed: 16920928]
15. Yu P, Kosco-Vilbois M, Richards M, Kohler G, Lamers MC. Negative feed back regulation of IgE synthesis by murine CD23. Nature 1994;369:753–6. [PubMed: 8008068]
16. Aubry JP, Pochon S, Graber P, Jansen KU, Bonnefoy JY. CD21 is a ligand for CD23 and regulates IgE production. Nature 1992;358:505–7. [PubMed: 1386409]
17. Capron M, Spiegelberg HL, Prin L, et al. Role of IgE receptors in effector function of human eosinophils. J Immunol 1984;132:462–8. [PubMed: 6228581]
18. Karanja DM, Boyer AE, Strand M, et al. Studies on schistosomiasis in western Kenya. II. Efficacy of praziquantel for treatment of schistosomiasis in persons coinfected with human immunodeficiency virus-1. Am J Trop Med Hyg 1998;59:307–11. [PubMed: 9715952]
19. Ganley-Leal LM, Mwinzi PN, Cetre-Sossah CB, et al. Higher percentages of circulating mast cell precursors correlate with susceptibility to reinfection with *Schistosoma mansoni*. Am J Trop Med Hyg 2006;75:1053–7. [PubMed: 17172364]
20. Ganley-Leal LM, Mwinzi PN, Cetre-Sossah CB, et al. Correlation between eosinophils and protection against reinfection with *Schistosoma mansoni* and the effect of human immunodeficiency virus type 1 coinfection in humans. Infect Immun 2006;74:2169–76. [PubMed: 16552047]
21. Lunde MN, Ottesen EA, Cheever AW. Serological differences between acute and chronic schistosomiasis mansoni detected by enzyme-linked immunosorbent assay (ELISA). Am J Trop Med Hyg 1979;28:87–91. [PubMed: 107819]
22. Weller S, Braun MC, Tan BK, et al. Human blood IgM “memory” B cells are circulating splenic marginal zone B cells harboring a prediversified immunoglobulin repertoire. Blood 2004;104:3647–54. [PubMed: 15191950]
23. Butterworth AE, Capron M, Cordingley JS, et al. Immunity after treatment of human schistosomiasis mansoni. II. Identification of resistant individuals, and analysis of their immune responses. Trans R Soc Trop Med Hyg 1985;79:393–408. [PubMed: 4035741]
24. Olveda RM, Daniel BL, Ramirez BD, et al. *Schistosomiasis japonica* in the Philippines: the long-term impact of population-based chemotherapy on infection, transmission, and morbidity. J Infect Dis 1996;174:163–72. [PubMed: 8655987]
25. Capron A, Dessaint JP. Effector and regulatory mechanisms in immunity to schistosomes: a heuristic view. Annu Rev Immunol 1985;3:455–76. [PubMed: 2933049]
26. Thompson C. IgE declares war on parasites. Lancet 1994;343:309–10. [PubMed: 7905141]
27. Woolhouse ME, Hagan P. Seeking the ghost of worms past. Nat Med 1999;5:1225–7. [PubMed: 10545976]
28. Sukumar S, Conrad DH, Szakal AK, Tew JG. Differential T cell-mediated regulation of CD23 (Fc epsilon RII) in B cells and follicular dendritic cells. J Immunol 2006;176:4811–7. [PubMed: 16585575]

29. Inaoki M, Sato S, Takehara K. Elevated expression of CD23 on peripheral blood B lymphocytes from patients with bullous pemphigoid: correlation with increased serum IgE. J Dermatol Sci 2004;35:53–9. [PubMed: 15194147]
30. Cabrera M, Rodriguez O, Monsalve I, Tovar R, Hagel I. Variations in the serum levels of soluble CD23, nitric oxide and IgE across the spectrum of American cutaneous leishmaniasis. Acta Trop 2003;88:145–51. [PubMed: 14516926]
31. Schwarzmeier JD, Shehata M, Hilgarth M, et al. The role of soluble CD23 in distinguishing stable and progressive forms of B-chronic lymphocytic leukemia. Leuk Lymphoma 2002;43:549–54. [PubMed: 12002758]
32. Stokes J, Casale TB. Rationale for new treatments aimed at IgE immunomodulation. Ann Allergy Asthma Immunol 2004;93:212–7. [PubMed: 15478378]
33. Hibbert RG, Teriete P, Grundy GJ, et al. The structure of human CD23 and its interactions with IgE and CD21. J Exp Med 2005;202:751–60. [PubMed: 16172256]
34. Flores-Romo L, Shields J, Humbert Y, et al. Inhibition of an in vivo antigen specific IgE response by antibodies to CD23. Science 1993;261:1038–41. [PubMed: 8351517]
35. Wilcock LK, Francis JN, Durham SR. IgE-facilitated antigen presentation: role in allergy and the influence of allergen immunotherapy. Immunol Allergy Clin North Am 2006;26:333–47. [PubMed: 16701148]
36. Payet-Jamroz M, Helm SL, Wu J, et al. Suppression of IgE responses in CD23-transgenic animals is due to expression of CD23 on nonlymphoid cells. J Immunol 2001;166:4863–9. [PubMed: 11290762]
37. Fluckiger AC, Briere F, Zurawski G, Bridon JM, Banchereau J. IL-13 has only a subset of IL-4-like activities on B chronic lymphocytic leukaemia cells. Immunology 1994;83:397–403. [PubMed: 7530690]
38. Punnonen J, Avera G, Cocks BG, et al. Interleukin 13 induces interleukin 4-independent IgG4 and IgE synthesis and CD23 expression by human B cells. Proc Natl Acad Sci USA 1993;90:3730–4. [PubMed: 8097323]
39. Leenstra T, Acosta LP, Wu HW, et al. T-helper-2 cytokine responses to Sj97 predict resistance to reinfection with *Schistosoma japonicum*. Infect Immun 2006;74:370–81. [PubMed: 16368992]
40. Fourie AM, Coles F, Moreno V, Karlsson L. Catalytic activity of ADAM8, ADAM15, and MDC-L (ADAM28) on synthetic peptide substrates and in ectodomain cleavage of CD23. J Biol Chem 2003;278:30469–77. [PubMed: 12777399]
41. Dierks SE, Bartlett WC, Edmeades RL, Gould HJ, Rao M, Conrad DH. The oligomeric nature of the murine Fc episilon RII/CD23: implication for function. J Immunol 1993;150:2372–82. [PubMed: 8450218]
42. Letellier M, Sarfati M, Delespesse G. Mechanisms of formation of IgE-binding factors (soluble CD23). I. Fc episilon R II bearing B cells generate IgE-binding factors of different molecular weights. Mol Immunol 1989;26:1105–12. [PubMed: 2534424]
43. Frémeaux-Bacchi V, Fischer E, Lecoanet-Henchoz S, Mani JC, Bonnefoy JY, Kazatchkine MD. Soluble CD21 (sCD21) forms biologically active complexes with CD23: sCD21 is present in normal plasma as a complex with trimeric CD23 and inhibits soluble CD23-induced IgE synthesis by B cells. Int Immunol 1998;10:1459–66. [PubMed: 9796912]
44. Schramm G, Mohres K, Wodrich M, et al. IPSE/alpha-1, a glycoprotein from *Schistosoma mansoni* eggs, induces IgE-dependent, antigen-independent IL-4 production by murine basophils in vivo. J Immunol 2007;178:6023–7. [PubMed: 17475824]

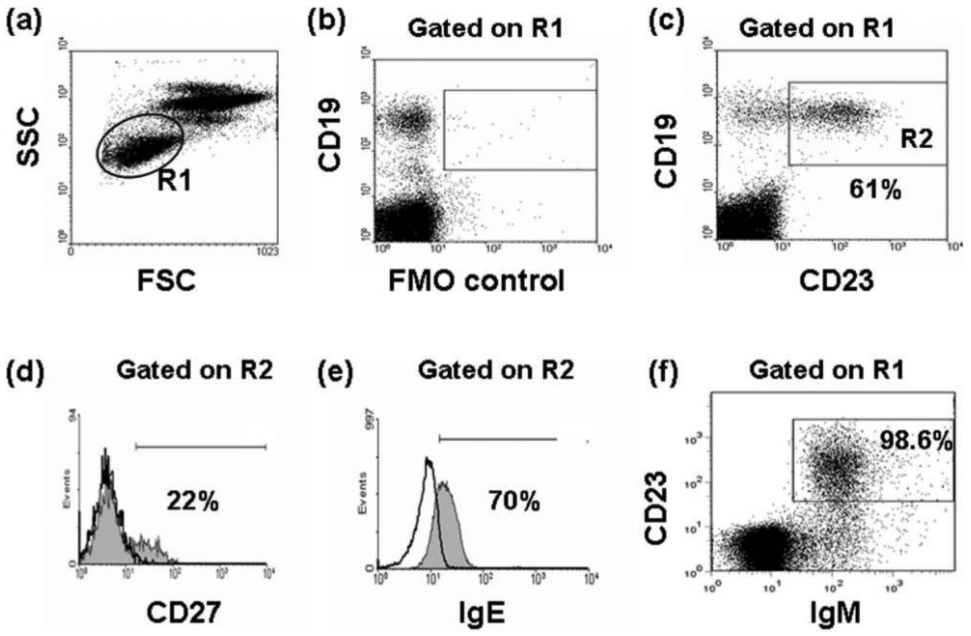

Figure 1.

CD23$^+$ B cells in human schistosomiasis. *a*, Flow cytometry analysis of whole-blood cells showing the R1 lymphocyte gate used for all subsequent analyses. Cells stained with anti-CD19 *(b)*, anti-CD23 *(c)*, anti-CD27 *(d)*, anti-IgE *(e)*, and anti-IgM *(f)* were used to define B cells and B cell subsets. CD19$^+$ B cells were analyzed in the R1 gate for positive CD23 expression *(c)*, using a threshold based on the fluorescence minus one (FMO) "no CD23-phycoerythrin" controls *(b)*. CD19$^+$CD23$^+$ B cells (gate R2) were analyzed for CD27 *(d)* and IgE *(e)* positivity against isotype controls. FSC, forward scatter; SSC, side scatter.

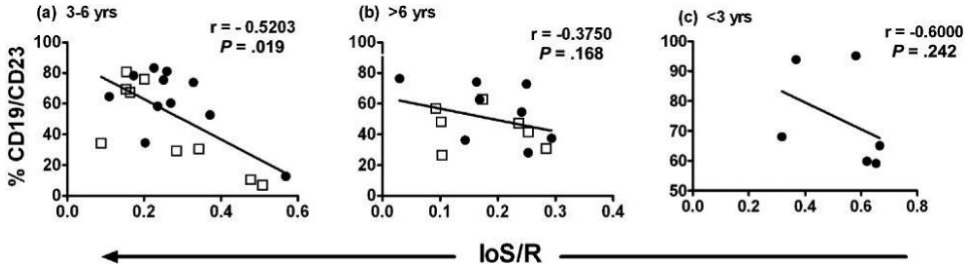

Figure 2.

Association between $CD23^+$ B cell levels and relative resistance to reinfection with *Schistosoma mansoni* in subjects followed up longitudinally for 3− 6 years *(a)*, >6 years *(b)*, or <3 years *(c)*. Percentages of $CD23^+CD19^+$ B cells, as assessed by flow cytometry, were plotted against the subjects' index of susceptibility/resistance (IoS/R) values, with results analyzed by Spearman's rank correlation test. Black circles and white squares represent data from HIV-1–seronegative and HIV-1–seropositive subjects, respectively.

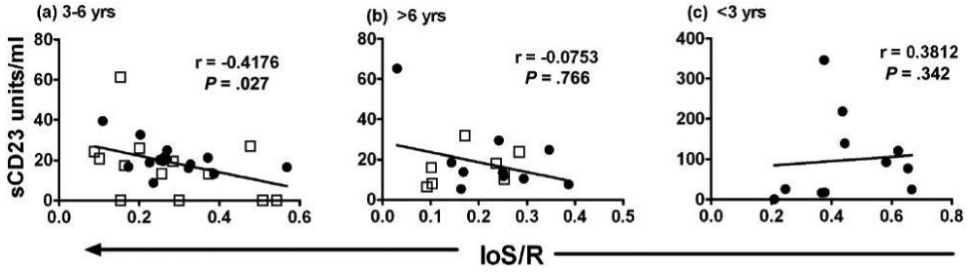

Figure 3.

Association between circulating levels of soluble CD23 (sCD23) and relative resistance to reinfection with *Schistosoma mansoni* in subjects followed up longitudinally for 3− 6 years *(a)*, >6 years *(b)*, or <3 years *(c)*. sCD23 levels, as determined by ELISA of plasma, were plotted against the subjects' index of susceptibility/resistance (IoS/R) values, with results analyzed by Spearman's rank correlation test. Black circles and white squares represent data from HIV-1–seronegative and HIV-1–seropositive subjects, respectively.

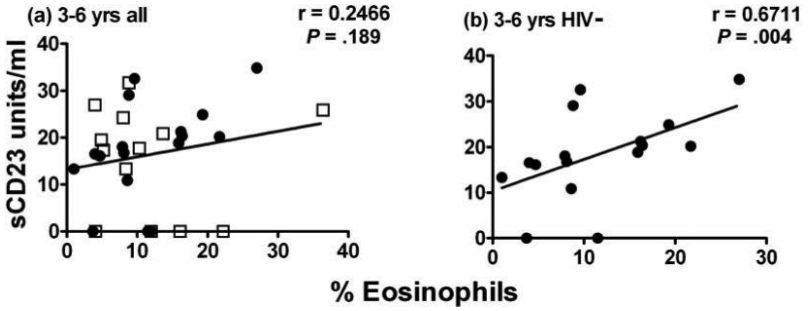

Figure 4.

Association between soluble CD23 (sCD23) and peripheral blood eosinophilia. Circulating sCD23 levels were determined and analyzed by Spearman's rank correlation test in relation to peripheral blood eosinophilia from the same blood sample, either for all subjects *(a)* or only for HIV-1–seronegative subjects *(black circles) (b)*. White squares represent HIV-1–seropositive subjects All subjects had been followed up for 3−6 years.

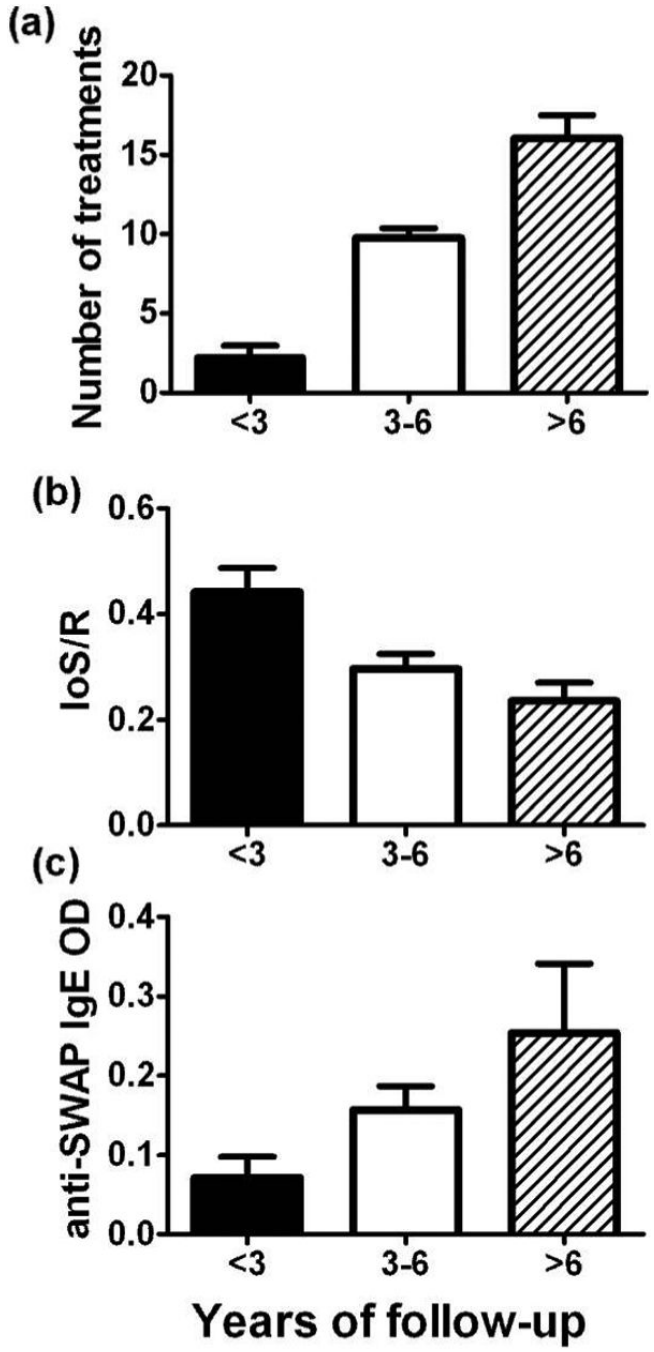

Figure 5.

Groups followed up for <3 years, 3−6 years, or >6 years compared with regard to the no. of treatments *(a)*, index of susceptibility/ resistance (IoS/R) values *(b)*, and anti–soluble worm antigenic preparation (SWAP) IgE levels *(c)*. Subjects underwent repeated praziquantel treatments whenever they became reinfected with *Schistosoma mansoni;* values are given as means ± SEs. The means for each of the 3 groups were analyzed by 1-way analysis of variance, followed by Dunn's posttest. In panel a, $P < .05$ for all comparisons between groups (P for trend, <.001); in panel b, $P < .05$ for the comparison between the <3-year and 3− 6-year groups and between the <3-year and >6-year groups (P for trend, <.001); in panel c, $P > .05$ for all comparisons between groups (P for trend, .032). OD, optical density.