Evolution of the Levels of Soluble Interleukin-2 Receptors during Plasmodium falciparum and P. vivax Malaria

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Increased levels of soluble interleukin-2 receptors (IL-2R) in serum were observed in both Plasmodium falciparum- and P. vivax-infected individuals compared with nonparasitic subjects. Clinical symptoms of P. falciparum malaria were associated with higher levels of soluble IL-2R. Temporal evolution in serum of IL-2R during the course of a malaria attack mimicked the kinetics of soluble IL-2R under experimental conditions.

Interleukin-2 is generally considered to play a pivotal role in the cellular immune response by regulating the proliferation of antigen-activated T lymphocytes expressing specific interleukin-2 receptors (IL-2R) on their surfaces (10). During the immune response, a soluble form of IL-2R is released by activated cells and can be detected in culture supernatants and serum (9). The precise immunoregulatory role of soluble IL-2R is unknown, but its increase has been demonstrated in various lymphoreticular diseases in which a strong immune reaction occurs (2, 4, 8). Levels of soluble IL-2R are also elevated in selected parasitic infections, including malaria (5, 7). We report here additional evidence of increased levels of IL-2R in Plasmodium falciparum and P. vivax malaria, as well as the results of a longitudinal study of the release in serum of these soluble receptors of IL-2.

Serum samples were collected in Madagascar during a cohort study (6). First, IL-2R was measured in samples collected from 95 individuals presenting with P. falciparum or P. vivax blood parasites and from nonparasitic individuals. No individual had presented with malaria parasites on the four previous weekly thick blood smears. Thirty-nine P. falciparum-infected individuals (parasite density, 16 to 320,000/µl; geometric mean parasite density, 2,993/µl) were studied. Nine had a symptomatic P. falciparum malaria, and thirty had an asymptomatic infection. Eighteen P. vivax-infected individuals (parasite density, 244 to 5,667/µl; geometric mean parasite density, 1,018/µl) were studied. Eight had a symptomatic infection, and ten had an asymptomatic infection. In both P. falciparum- and P. vivax-infected individuals, parasite densities were similar in symptomatically and asymptotically infected individuals. Thirty-eight healthy, nonparasitic individuals were studied. All individuals were 10 to 62 years old; the mean ages of P. falciparum- and P. vivax-infected individuals and of those who were non-parasitic were similar (29.2 ± 12.9 years). Sex ratios were also similar (male/female ratio, 0.63) in all three groups of individuals.

In addition, IL-2R was measured in serum samples collected every 2 weeks for 4 weeks from 28 subjects. At the first (W-2) and last (W+2) serum collections, all individuals presented with a negative blood smear. At the second collection of serum (W0), 12 individuals were infected with P. falciparum (4 had clinical symptoms). 10 were infected with P. vivax (4 had clinical symptoms), and 6 were nonparasitic.

The level of soluble IL-2R was measured by a commercially available sandwich immunossay (T Cell Sciences, Cambridge, Mass.) using two monoclonal antibodies that recognized different epitopes on the IL-2R molecule. Serum samples were diluted 1:3 (and in some instances 1:30). The resulting A 490 was measured. A standard curve was determined with four reference samples and used to calculate soluble IL-2R concentrations (units per milliliter) in the serum samples. Comparisons between groups were done by analysis of variance and by Student’s t tests for independent samples.

In the transversal study, the three groups of subjects exhibited different levels of serum IL-2R (P < 0.0001) (Fig. 1). The IL-2R levels were similar in individuals infected with P. falciparum (range, 480 to 4,200 U/ml; mean, 1,409 ± 681 U/ml) and P. vivax (range, 420 to 2,600 U/ml; mean, 1,384 ± 579 U/ml) and were lower in nonparasitic individuals (range, 220 to 1,110 U/ml; mean, 662 ± 217 U/ml) (for both, P < 0.0005). Among P. falciparum-infected subjects, higher levels of IL-2R were observed in those with clinical symptoms of malaria (range, 700 to 4,200 U/ml; mean, 1,804 ± 1,147 U/ml) than in those with no symptoms (range, 480 to 2,170 U/ml; mean, 1,291 ± 427 U/ml) (P < 0.5). This difference was not observed among P. vivax-infected individuals. No correlation was observed between IL-2R levels and parasite counts or age of the subjects.

The W-2 serum IL-2R levels of the 28 subjects who were monitored longitudinally (range, 300 to 1,110 U/ml; mean, 685 ± 216 U/ml) were similar to the levels of the 38 noninfected individuals previously studied. No temporal variation of soluble IL-2R was observed in the six individuals who remained nonparasitic (Fig. 2). Ten of the twelve subjects who developed a P. falciparum infection exhibited a rise in their IL-2R serum level at W0, and nine of those ten exhibited a subsequent decline at W+2. Similar evolution occurred in 9 of the 10 individuals infected with P. vivax. The three remaining subjects had similar levels of IL-2R at W-2 and W0, but this level rose in two of them (one infected with P. falciparum and one with P. vivax) at W+2.

Levels of soluble IL-2R in serum increased in both P. falciparum and P. vivax malaria. With P. falciparum malaria, this level was higher in subjects with clinical symptoms of the disease than in those with no symptoms. With P. vivax malaria we did not observe a similar relationship. However,
FIG. 1. Levels of soluble IL-2R in serum from individuals with a *P. falciparum* or *P. vivax* malaria infection and in nonparasitemic controls. The arrows indicate the mean value of serum IL-2R in each group.

FIG. 2. Evolution of the level of soluble IL-2R in serum during the course of a *P. falciparum* or *P. vivax* malaria infection and in noninfected controls.
the number of investigated subjects was small, and none were suffering from a severe malaria attack. Whether the malaria-associated symptomatology originates from or is a consequence of the immune response remains to be determined.

Our longitudinal study gives further evidence of the role of malaria in the release of IL-2R in serum of infected subjects. The temporal evolution of IL-2R levels in the sera of malaria-infected subjects mimics the kinetics of IL-2R observed under experimental conditions, as reported by Cantrell and Smith (1). Following activation of peripheral mononuclear cells by phytohemagglutinin, IL-2R was detected at its maximum level within 3 to 4 days and declined to a very low level after 2 weeks of culture. All but one subject with increased IL-2R during infection exhibited IL-2R levels within the normal range 2 weeks later. Conversely, two infected subjects had similar levels of IL-2R at W0 and W-2 but raised levels at W+2. In these two subjects, parasites might have proliferated in blood for too short a time prior to the W0 blood collection to allow expression and release of IL-2R in serum. Such a phenomenon might also have happened in some individuals in the transversal study. The last subject who showed no variation in serum IL-2R may have had either an unknown rise and decline of IL-2R (between W0 and W+2) or a lack of the immune response originating expression or release of IL-2R.

Increase in soluble IL-2R in *P. falciparum* and *P. vivax* malaria probably reflects antigen-specific lymphocyte activation and clonal expansion. The level of IL-2R may be used to study the responses of the involved cellular subpopulations (which remain to be determined). High circulating levels of IL-2R might be able to bind interleukin-2 and be responsible for the immunosuppression observed during the acute phase of malaria. Whether this increase has beneficial or negative (as tumor necrosis factor [3]) effects also remains to be clarified.

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**LITERATURE CITED**


