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Immunoglobulin E, a Pathogenic Factor in *Plasmodium falciparum* Malaria

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Most children and adults living in areas where the endemicity of *Plasmodium falciparum* malaria is high have significantly elevated levels of both total immunoglobulin E (IgE) and IgE antimalarial antibodies in blood. This elevation is highest in patients with cerebral malaria, suggesting a pathogenic role for this immunoglobulin isotype. In this study, we show that IgE elevation may also be seen in severe malaria without cerebral involvement and parallels an elevation of tumor necrosis factor alpha (TNF). IgE-containing serum from malaria immune donors was added to tissue culture plates coated with rabbit anti-human IgE antibodies or with *P. falciparum* antigen. IgE–anti-IgE complexes as well as antigen-binding IgE antibodies induced TNF release from peripheral blood mononuclear cells (PBMC). Nonmalaria control sera with no IgE elevation induced significantly less of this cytokine, and the TNF-inducing capacity of malaria sera was also strongly reduced by passing them over anti-IgE Sepharose columns. The cells giving rise to TNF were adherent PBMC. The release of this cytokine probably reflects cross-linking of their low-affinity receptors for IgE (CD23) by IgE-containing immune complexes known to give rise to monocyte activation via the NO transduction pathway. In line with this, adherent monocytic cells exposed to IgE complexes displayed increased expression of CD23. As the malaria sera contained IgG anti-IgE antibodies, such complexes probably also play a role in the induction of TNF in vivo. Overproduction of TNF is considered a major pathogenic mechanism responsible for fever and tissue lesions in *P. falciparum* malaria. This overproduction is generally assumed to reflect a direct stimulation of effector cells by certain parasite-derived toxins. Our results suggest that IgE elevation constitutes yet another important mechanism involved in excessive TNF induction in this disease.

We have previously reported that approximately 85% of children and adults living in areas of The Gambia, Liberia, Madagascar, or Thailand in which *Plasmodium falciparum* malaria is endemic have elevated levels in blood of immunoglobulin E (IgE), comprising both total IgE and IgE antimalaria antibodies (33). Similar findings have earlier been reported from Papua New Guinea (12, 13). In general, elevated concentrations of IgE in serum reflect an underlying imbalance in the ratio of T-helper cells, in favor of the Th2 variety producing the cytokines (interleukin-4 [IL-4] and IL-13) primarily responsible for Ig isotype switching to IgE (15, 37). This imbalance could reflect preceding or concomitant infections with other parasites such as helminths. However, as it has been shown that experimental infection of mice of certain haplotypes with *Plasmodium chabaudi chabaudi* also induces IgE elevation (19, 45), it is likely that IgE elevation in human *P. falciparum* infection is usually (although perhaps not always) caused by this parasite without any "help" from other pathogens.

IgE may have both protective and pathogenic effects in infectious diseases. A possible pathogenicity in malaria was suggested by the finding of significantly higher IgE levels in patients with cerebral malaria than in those with uncomplicated *P. falciparum* infections (33). The pathogenesis of cerebral malaria, involving impaired consciousness, unrousable coma, and various neurological abnormalities, is poorly understood (46). However, two major but not mutually exclusive causes are usually implicated, one involving obstruction of blood flow due to sequestration of parasitized erythrocytes to postcapillary venules of the brain and the other being the effects on brain tissue of mediators such as tumor necrosis factor alpha (TNF) and NO, induced by parasite-derived material (9, 31). It is generally agreed upon that the cytokine TNF is one of the important factors involved in the severity of disease in *P. falciparum* infection (17, 26).

IgE complexed with antigen or with anti-IgE IgG may efficiently induce release of both TNF and NO from certain cell types equipped with Fc receptors for this Ig isotype (14). Of the two major Fc_ε receptors, the high-affinity receptor $Fc_\varepsilon RI$, occurring primarily on mast cells and basophils, is involved in mediating IgE-dependent allergic responses (4). In contrast, the low-affinity $Fc_\varepsilon RII$ or CD23 has been shown to mediate IgE-dependent effector functions such as cellular cytotoxicity and phagocytosis (6). CD23 is a type II membrane glycoprotein of the C-type lectin family (11). It is expressed on a variety of cell types, including monocytes/macrophages, eosinophils, platelets, and B lymphocytes. Its expression on monocytes is induced by cytokines such as IL-4 (42) and correlates with IgE elevation occurring in the course of an immune response (10, 23, 43).

IgE interaction with CD23-carrying effector cells is assumed to play an important although controversial role in protection

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TABLE 1. IgE in the blood of donors with uncomplicated or cerebral *P. falciparum* malaria

Origin	Amt of IgE in sample				P^c
	Uncomplicated		Cerebral		
	No.[a]	Concn[b]	No.	Concn	
Sudan	12	187 ± 61	19	737 ± 161	0.01
Ethiopia	15	143 ± 26	15	413 ± 125	0.04

[a] Number of donors.
[b] In nanograms per milliliter plus or minus standard error.
[c] Unpaired *t* test.

against helminthic infections (7, 18, 36). For malaria no direct evidence regarding IgE's possible protective or pathogenic functions is presently available. In this paper we have approached some of these problems by looking for possible associations between IgE elevation and TNF in the blood of malaria-exposed individuals and by investigating the potential of their sera to induce TNF in monocytes. The results suggest that IgE elevation in *P. falciparum* malaria is of pathogenic significance for severe and cerebral malaria and probably for *P. falciparum* infection in general. However, this does not exclude the possibility that some IgE antimalarial antibodies also have important protective functions.

MATERIALS AND METHODS

Sera. Venous blood samples were obtained from children and adults living in areas in Sudan, Ethiopia, The Gambia, Tanzania, and Senegal where malaria is endemic. The samples from Sudan and Ethiopia were obtained from hospitalized patients with diagnosed acute severe or uncomplicated *P. falciparum* malaria. Those from The Gambia (Brefet village), Tanzania (Muheza district), and Senegal (Dielmo, south Senegal) were obtained from immune donors with no clinical malaria at the time of sampling. Swedish donors who never experienced malaria were used as controls. Some sera were depleted of IgE by adding an immunosorbent of rabbit anti-IgE antibodies coupled to Sepharose (5 mg of rabbit IgG, 2 ml of cyanogen bromide Sepharose 43; Pharmacia LKB Biotechnology AB, Uppsala, Sweden). For depletion, 1 ml of serum diluted 1:50 was absorbed twice with ~30 μl of immunosorbent for 1 h at 4°C.

Cell cultures. Peripheral blood mononuclear cells (PBMC) from healthy Swedish donors were isolated by Ficoll-Paque (Pharmacia LKB Biotechnology AB, Uppsala, Sweden) density gradient centrifugation as described previously (41). Adherent cells were enriched by incubation of PBMC in tissue culture flasks for 90 min at 37°C with medium containing 50% autologous plasma. Nonadherent cells were washed off, and adherent cells were recovered after overnight incubation at 4°C. Cell cultures were run in flat-bottom tissue culture plates under normal tissue culture conditions (41) with either 200,000 unfractioned PBMC/well, 200,000 PBMC depleted of adherent cells, or 100,000 PBMC enriched in adherent cells.

TNF induction. Before addition of the cells, the wells of tissue culture plates were coated at 4°C overnight with a rabbit IgG antibody specific for human IgE. African sera or Swedish control sera diluted 1:100 were then added, and the plates were incubated at room temperature overnight to allow for binding of IgE to the anti-IgE antibodies. The cells were then added for 20 to 24 h at 37°C. The culture supernatants were withdrawn and analyzed for TNF by enzyme-linked immunosorbent assay (ELISA), as described below. In other experiments, anti-human IgE was omitted. Instead, the wells were coated with a synthetic multiple antigenic peptide containing four branches of the sequence INKRKYDSLKEKL (one-letter code), corresponding to positions 202 to 216 in the *P. falciparum* blood stage antigen Pf155/RESA (33, 39a).

ELISA. Total serum IgE was determined in ELISA plates coated with affinity-purified rabbit IgG antibodies specific for human IgE (5 μg/ml; Miab, Uppsala, Sweden). For determining antimalarial IgE antibodies, the plates were coated at 4°C overnight with 50 μl of Percoll fractionated parasite antigen (10 μg/ml) per well or with the synthetic malaria peptide (5 μg/ml) mentioned in the preceding paragraph (33). The test sera were diluted 1:1,000 for assay of total IgE and 1:50 for that of IgE antibodies. As detection of IgE antibodies in the presence of an excess of IgG antibodies requires prolonged interaction times (33) incubation was at room temperature overnight. Bound IgE was assayed with biotinylated, IgE-specific rabbit antibodies followed by alkaline phosphatase (ALP)-conjugated streptavidin (Mabtech, Stockholm, Sweden) as described in detail elsewhere (33). For determining IgG anti-IgE antibodies, the plates were coated with anti-IgE as above but assayed with ALP-conjugated, IgG-specific rabbit antibodies (Fc_γ specific; Dakopatts, Glostrup, Denmark). The test sera were diluted 1:500. Concentrations were calculated from standard curves obtained by incubating serial dilutions of a purified myeloma IgE or serum IgG in the wells coated with Fc_ε- or Fc_γ-specific antibodies and assayed as described above. For determination of TNF, the ELISA plates were coated with a purified mouse anti-human TNF monoclonal antibody (clone MAb 1; Pharmingen, San Diego, Calif.). Frozen, not previously thawed sera were analyzed at a dilution of 1:2; cell culture supernatants were assayed undiluted. Bound TNF was determined with biotinylated anti-human TNF antibodies (Pharmingen) followed by ALP-conjugated streptavidin (Mabtech). A TNF standard (NIBSC) was used for quantification at concentrations of 0.01 to 3 ng/ml.

Immunofluorescence. For detection of CD23 (Fc_εRII), PBMC (see "Cell cultures" above) were allowed to adhere to adhesion slides and then stained with fluorescein isothiocyanate-conjugated mouse anti-human CD23 monoclonal antibody (MHM6; Dakopatts).

RESULTS

Previous studies of a large group of Gambian children indicated that most of them had significantly elevated blood IgE concentrations. Moreover, in the blood of children with cerebral malaria, IgE elevation but not that of IgG was significantly higher than what was seen in age-matched controls with uncomplicated disease (33). Recent extension of these studies to other geographic areas included in this study fully confirmed these findings (Table 1). As previously reported, a fraction (1 to 5%) of this IgE represents antibodies to *P. falciparum* (33). Figure 1 shows that the concentration of IgE antimalarial antibodies in patients with cerebral malaria also was higher than that in patients with uncomplicated disease ($P < 0.01$, unpaired *t* test).

It is well established that patients suffering from malaria also have elevated levels in blood of TNF, a major factor causing malaria fever and closely associated with disease severity (16, 25, 27). This is illustrated in Table 2, showing the results obtained with a small but representative group of donors with either uncomplicated or severe (but not cerebral) *P. falciparum* malaria. As may be seen, severe disease without cerebral involvement was also associated with an increase of serum TNF concentration as well as with an increase in IgE.

TNF is produced by many cells, including endothelial cells, monocytes, and other hematopoietic cells (1). It has recently been recognized that one of the reactions leading to TNF generation by activated mononuclear phagocytes is cross-linking of CD23, their low-affinity receptor (Fc_εRII) for IgE (5, 14,

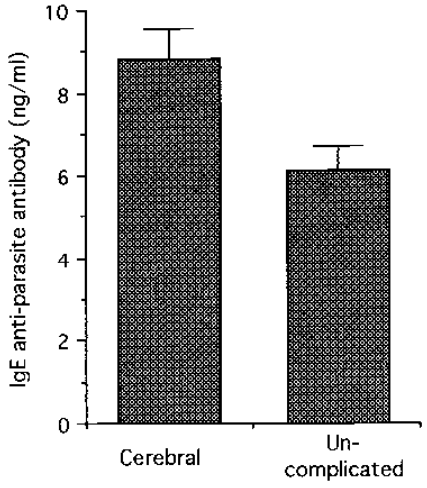

FIG. 1. IgE antibodies to *P. falciparum* blood stage antigens in sera from 15 Ethiopian donors with uncomplicated malaria and 15 with cerebral malaria.

TABLE 2. Concentrations of IgE or TNF in sera from Sudan

Donor type	*n*	Amt ± SE	
		IgE[a]	TNF[b]
Uncomplicated malaria	9	222 ± 63	147 ± 93
Severe malaria	6[c]	582 ± 151[d]	492 ± 108[e]

[a] In nanograms per milliliter.
[b] In picograms per milliliter.
[c] No cerebral involvement.
[d] $P = 0.03$ (unpaired t test).
[e] $P = 0.04$ (unpaired t test).

TABLE 3. TNF induction in mononuclear cells

Inducer[a]	Expt 1 (Ig isotype)[b]		Expt 2 (PBMC reactions)[c]	
	Anti-IgE	Anti-IgG	Adherent	Nonadherent
Malaria sera	715 ± 46	414 ± 21	297 ± 40	50
Control sera	345 ± 21	457 ± 87	180 ± 10	40

[a] Malaria sera were from 25 repeatedly *P. falciparum*-infected Tanzanian and Senegalese donors. None of the donors had clinical disease at the time of sampling. Control sera were from Swedish donors never exposed to malaria.
[b] Results are in picograms per milliliter for 2×10^5 mononuclear cells, plus or minus standard error. Difference between malaria and control sera, $P = 0.003$ (anti-IgE) and $P = 0.48$ (not significant) (anti-IgG) (unpaired t test).
[c] Results are in picograms per milliliter for 10^5 mononuclear cells, plus or minus standard error. The background in the absence of cells was 25 pg of TNF per ml. Difference (for adherent cells) between malaria and control sera, $P = 0.005$ (unpaired t test).

43). In order to establish if such a mechanism could be involved in the pathogenesis of malaria, the wells of microtitration plates were coated with rabbit antibodies to IgE, followed by the addition of either IgE-containing malaria sera or control sera with no IgE elevation. After incubation to allow IgE binding to the wells, PBMC from normal donors were added and the supernatants were then assayed for TNF. All sera gave rise to some TNF release, probably reflecting the presence of some bacterial lipopolysaccharides, as no measures had been taken to remove these. However, the IgE-containing sera consistently induced more TNF than the control sera (Fig. 2). This difference was statistically highly significant ($P = 0.0001$, unpaired t test, seven experiments). Thus far, approximately 40 sera of each kind have been assayed either as pools or individually. In contrast, no differences between malaria sera or control sera were seen when the plates had been coated with rabbit anti-human IgG antibodies (Table 3, experiment 1).

When the plates were coated with a synthetic peptide representing a conserved epitope of a major *P. falciparum* blood stage antigen, addition of malaria serum and normal PBMC also gave rise to release of TNF. As seen from Fig. 3, this release was well correlated with the content of these sera of IgE antimalaria antibodies binding to the test antigen ($r = 0.6$, $P = 0.036$; F test; results not shown). No correlation was seen for IgG antibodies ($r = 0.2$, $P = 0.507$; F test). That TNF induction by malaria serum reflects the effect of the formation of IgE–anti-IgE complexes was also supported by the inclusion of a myeloma IgE serving as positive control (not shown).

Separation of PBMC into adherent and nonadherent fractions confirmed that the mononuclear cells releasing TNF in anti-IgE-coated plates were entirely confined to the adherent fractions (Table 3, experiment 2). When IgE–anti-IgE-exposed PBMC were studied after 2 to 5 days of incubation by immunofluorescence with a monoclonal anti-CD23 antibody, from 50 to 80% of the adherent monocytic cells developed strong surface staining, culminating at day 5 (results not shown). The results were in line with the fact that CD23 expression is strongly enhanced by exposure of cytokine-activated cells to IgE-containing immune complexes (14, 23, 43).

The importance of IgE-containing complexes for the induction of TNF was further supported by experiments with IgE-depleted malaria sera. As shown in Fig. 4, IgE depletion significantly reduced their capacity to release TNF ($P < 0.01$, paired t test) when they were added to anti-IgE-coated plates together with PBMC. That immune complexes formed by the donors' own anti-immunoglobulin also may give rise to TNF induction in malaria patients in vivo was suggested by assaying malaria sera for IgG anti-IgE antibodies. A representative sample of 11 Gambian malaria sera having high total IgE and 11 having low total IgE concentrations in Table 4 shows that they contained considerable amounts of IgG binding specifically to the anti-IgE-coated plates. No IgE-binding IgG was found in control sera (not shown). We have seen IgG anti-IgE antibodies in all IgE-containing malaria sera investigated thus far.

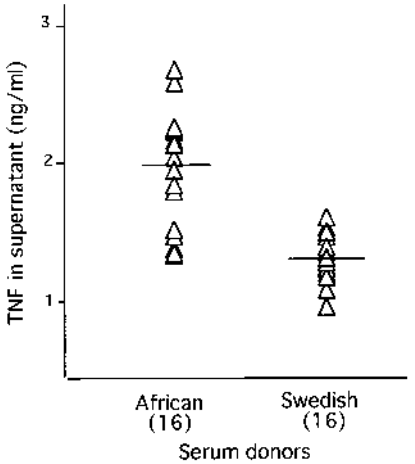

FIG. 2. Induction of TNF from PBMC incubated with African sera (8 from Tanzania, 8 from Senegal) or Swedish control sera in microtitration plates coated with rabbit anti-human IgE antibodies.

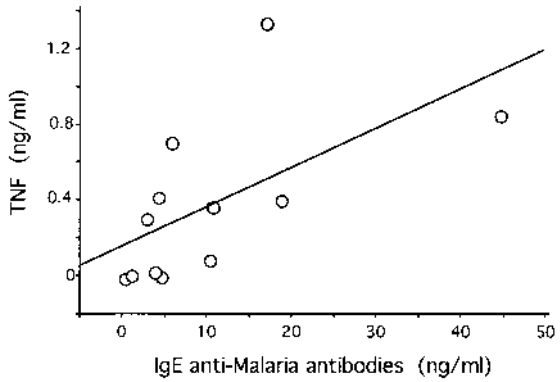

FIG. 3. Correlation of TNF release from PBMC to concentration of IgE antimalaria antibodies in 12 Tanzanian sera. For TNF induction, the sera and cells were incubated in microtitration plates coated with a multiple antigenic peptide (INKRKYDSLKEKL, 4 branches) corresponding to an epitope at position 202 to 216 of the antigen Pf155/RESA (33, 39a).

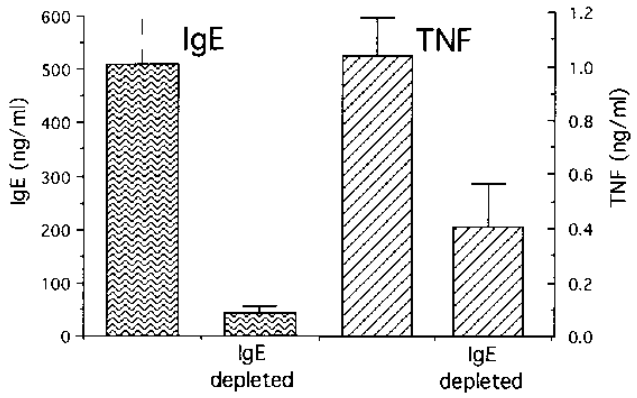

FIG. 4. Effects of IgE depletion on TNF release from PBMC. Six Tanzanian and four Senegalese sera were depleted of IgE by two incubations with an anti-IgE immunosorbent as described in Materials and Methods. For TNF induction, the absorbed sera (final dilution, 1:100) and PBMC were incubated for 20 h on anti-IgE-coated microtitration plates.

DISCUSSION

The results reported in this paper support the conclusion that the elevation of IgE in human *P. falciparum* malaria may be instrumental in the pathogenesis of this disease. Although the basis of these studies was our initial finding that IgE elevation was most pronounced in sera from patients with cerebral malaria (33), the data presented here suggest that IgE may be considered a pathogenic factor in severe disease without cerebral involvement and, probably, in *P. falciparum* malaria in general. Such conclusions do not exclude the possibility that IgE antibodies, by cooperating with Fc_ε-receptor-bearing cells, also protect against malaria infection. This is a controversial issue for helminthic infections, where the occurrence of IgE elevation has been known for a long time (7, 18, 36). The question of IgE's possible protective effects in malaria is under investigation (see also below).

There is no evidence indicating that the pathogenic effects of IgE in malaria reflect activities of antibodies specific for parasite antigens associated with severe disease (33). Rather, the results suggest that disease severity is correlated with IgE concentration in general and that the mechanisms triggering pathogenicity in vivo involve interaction of IgE with $Fc_\varepsilon R$-bearing effector cells. In the system studied herein, these were mononuclear phagocytes. When activated by such interactions, these cells produce a variety of cytokines, including TNF (14, 43), which is a protective factor in malaria (8, 24, 30) but, when produced in excessive amounts, causes fever and tissue lesions involved in pathogenesis (16, 25).

Although monocytes from atopic patients have recently been shown to also express high-affinity Fc_ε receptors ($Fc_\varepsilon RI$), CD23 (or $Fc_\varepsilon RII$) appears to be the major factor linking TNF induction to IgE (14, 23). This low-affinity IgE receptor has a wide cellular distribution (10). It is also an adhesion molecule mediating cellular interactions independently of IgE (28). It is poorly expressed on human monocytes in the resting stage (42), but, as also seen in this investigation, expression is strongly enhanced when the cells are exposed to IgE-containing immune complexes (14, 20). Its cross-linking by IgE or other ligands also results in induction of cytokine production via the nitric oxide transduction pathway (10, 14). The latter appears to be of major significance in mediating killing of intracellular parasites (32, 39, 44). Obviously, the IgE-mediated cross-linking of CD23 leading to activation of inducible nitric oxide synthase and NO production could be an important protective mechanism in plasmodial infection. At the same time, it should be noted that NO may contribute to the pathogenesis of cerebral malaria (9) and perhaps other severe forms of the disease.

TNF transcription is genetically regulated (29), and its overproduction is associated with disease severity and is even predisposing for a fatal outcome of *P. falciparum* malaria (16, 26). Nevertheless, it is clear that excessive TNF is not on its own sufficient to explain the relatively rare occurrence of severe disease. Thus, other plasmodial infections which are not associated with increased mortality or cerebral disease may induce peak levels of plasma TNF surpassing those seen in *P. falciparum* infection (17, 22). This implies that additional factors contribute to disease severity in *P. falciparum* infection. Of major importance is the capacity of *P. falciparum*-infected erythrocytes to sequester by adhering to endothelial cells lining capillaries and postcapillary venules (3, 20). This sequestration will also contribute to the deposition of IgE in basement membranes of cerebral capillaries as seen in autopsy material from patients with cerebral malaria (2). Such IgE deposits may contain malaria antigen and/or consist of IgE complexed with IgG anti-IgE antibodies, which, as shown here, also occur at elevated levels in *P. falciparum* malaria. Regardless of their composition, by activating passing monocytes or, perhaps, CD23-expressing vascular endothelial cells, these deposits may induce local overproduction of TNF as well as NO and thereby contribute to the pathogenesis of cerebral *P. falciparum* malaria (9). Similar mechanisms could perhaps also be implicated

TABLE 4. Total IgE and IgG anti-IgE antibodies in the blood of malaria-immune donors

IgE concn[a]	Total IgE (μg/ml)	IgG anti-IgE (ng/ml)
High	14.99	5,677
	18.87	1,818
	26.02	1,636
	10.24	1,451
	52.80	1,141
	35.93	1,070
	27.35	867
	14.03	564
	21.18	391
	19.73	73
	10.78	55
Mean	27.90	1,340
Low	0.11	849
	0.94	458
	1.67	379
	0.34	303
	0.39	291
	1.97	211
	0.85	160
	0.03	89
	0.48	87
	0.28	36
	1.20	33
Mean	0.75	263

[a] Sera were from 22 Gambian donors, repeatedly infected with *P. falciparum* but with no clinical disease at the time of sampling. The sera were arbitrarily divided into two groups having high (>10 μg/ml) or low (<2.0 μg/ml) concentrations of total IgE.

in the pathogenicity of severe *P. falciparum* malaria without cerebral involvement.

The release of TNF from activated monocytes/macrophages or endothelial cells may be set in motion by their direct interaction with a variety of agents including parasite antigens or pigment (34, 35). In particular, parasite-derived toxins containing glycosyl-phosphatidyl inositol anchor structures are believed to be primarily responsible for TNF induction (21, 38, 40). The results reported herein point to yet another important mechanism which links TNF to the levels of IgE produced in the course of the antiplasmodial immune response. Further work is needed to establish the relative role of IgE in relation to other TNF-inducing reactions in the pathogenesis of *P. falciparum* malaria.

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