LOCALIZATION OF A MOLECULE IMMUNOCHEMICALLY SIMILAR TO EOSINOPHIL MAJOR BASIC PROTEIN IN HUMAN PLACENTA

BY DANIEL E. MADDOX, GAIL M. KEPHART, CAROLYN B. COULAM, JOSEPH H. BUTTERFIELD, KURT BENIRSCHKE,* AND GERALD J. GLEICH

From the Allergic Diseases Research Laboratory and the Departments of Immunology, Medicine, and Obstetrics and Gynecology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55905; and the *Department of Pathology, University of California at San Diego, San Diego, California 92093

The eosinophil granule major basic protein (MBP) is an arginine rich, highly basic, 9,300 dalton protein, which forms the crystalloid core of the granule (1-3) and is present in small amounts in basophils (4). MBP is toxic to parasites (5-7) and is deposited onto the surface of damaged microfiliariae in Onchocerca volvulus infestation (8). MBP is also toxic to cells (5, 9) and causes desquamation of respiratory epithelial cells in vitro (10, 11). Finally, MBP triggers histamine release from human basophils and rat mast cells (12).

We have recently reported that MBP circulates in the blood of pregnant women at levels 10 to 20 times those found in normal, nonpregnant women (13). The levels of this immunoreactive MBP increase during the first 3 mo of gestation, plateau during the second and third trimester, and decrease sharply following parturition. Eosinophilia is not present during pregnancy, and other eosinophil-related proteins are not elevated in the sera of pregnant women. Chromatographic analysis of sera from pregnant women indicates that the immunoreactive MBP has an apparent molecular size greater than the molecule purified from the eosinophil granule. These observations suggest that the immunoreactive MBP molecule in the sera of pregnant women is derived from a source other than the eosinophil. Here we report that immunoreactive MBP is localized in placenta, intracellularly in placental X cells and placental-site giant cells and extracellularly in anchoring villi and at the choriordecidual junction.

Materials and Methods

Tissue. Placental tissue was prepared in the delivery suite for fixation and embedding. First and second trimester medical abortion tissues were kindly provided by Dr. M. Hansen, Minneapolis, MN. Other placental and gestational tissues were available from the Department of Pathology of the Mayo Clinic. Table I lists the types of tissues and the number of blocks examined from each.

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Abbreviations used in this paper: MBP, eosinophil granule major basic protein; PBS, phosphate-buffered saline; HE, hematoxylin and eosin.
TABLE I

Tissues Examined for MBP by Immunofluorescence

| Clinical diagnosis            | Number of cases | Tissue                                      | Number of blocks examined |
|------------------------------|-----------------|---------------------------------------------|---------------------------|
| Normal gestation             | 14              | Placenta                                    | 53                        |
|                              |                 | Umbilical cord                              | 6                         |
| Tubal pregnancy              | 2               | Fallopian tube with conceptus               | 17                        |
|                              |                 | Concurrent endometrium                      | 2                         |
| Medical abortion             | 14              | Placenta                                    | 14                        |
| Spontaneous abortion         | 1               | Placenta                                    | 3                         |
| Hydatidiform mole            | 2               | Uterine curettings                          | 4                         |
| Choriocarcinoma              | 1               | Placenta                                    | 3                         |
| Miscellaneous*               | 37              | Uterine curettings                          |                           |

* This category includes placental tissues from single or few cases of severe pre-eclampsia, twins, pruritic urticarial plaques and papules of pregnancy (PUPPP) syndrome, fetal anencephaly, placenta accreta, placental abruption, and retained placenta; other tissues included endometriosis (hysterectomy specimen) and maternal skin.

Immunofluorescence Localization of MBP. The indirect immunofluorescence method has been described in detail (14-16). Briefly, formalin-fixed, paraffin-embedded tissue was sectioned at 6 μm and glued to glass microscope slides. Sections were deparaffinized, rehydrated, and digested with trypsin. Tissues were washed and incubated under 10% normal goat serum to inhibit nonspecific interactions between second stage reagents and the tissue. They were incubated with either affinity-purified rabbit anti-MBP antibody or protein A affinity-purified normal rabbit IgG as a control, followed by washing, treatment with chromotrope 2R to prevent nonspecific eosinophil fluorescence, repeat washing, and exposure to the second stage goat anti-rabbit Ig antibody conjugated with fluorescein isothiocyanate. After a final wash, sections were sealed under coverslips, using a glycerol/phosphate-buffered saline (PBS) (9:1) mounting medium made 10 mg/ml in para-phenylenediamine to inhibit fluorescence fading. Immunofluorescence microscopy used a Zeiss microscope fitted with Zeiss IV FL vertical illumination for epifluorescence and a fluorescein filter system (Carl Zeiss, Inc., Thornwood, NY). In some instances, sections showing positive immunofluorescence were photographed, the coverslip was soaked off, the section was counterstained with hematoxylin and eosin (HE), and areas of interest were photographed again to permit direct correlation between fluorescent structures and conventional histologic landmarks. Photomicrography was carried out using Kodak Ektachrome 400 ASA slide film (fluorescence) or Kodak Ektachrome 64 ASA slide film (HE counterstains) in a Zeiss M35 camera back mounted with power winder. The exposure time for fluorescence was 60 s.

Giemsa Staining for Eosinophils. Tissue specimens were processed as described by Godfrey et al. (17) to determine whether eosinophils were present in placenta. Briefly, fresh tissue was reduced by sharp dissection to 2-mm cubes, immersed in Karnovsky's fixative (18) for 2 h at room temperature, and incubated in the cold overnight in 0.2 M cacodylate buffer. Fixed tissue was embedded in methacylate and 2-μm sections were cut and mounted on glass slides. Sections stained with Giemsa at pH 6.5 were examined by light microscopy.

Extraction of MBP from Placental Tissue. Placental extracts were obtained as summarized in Table II. Tissue was prepared for extraction by mincing fresh tissue with a scissors, until cubes of approximately 2-4 mm were obtained. To remove maternal blood, minced tissue was washed on stainless steel sieves (U. S. Standard mesh No. 100) with cold saline until the effluent was clear. After weighing, tissue was homogenized in a glass-
TABLE II

 CONDITIONS FOR EXTRACTION OF MBP FROM PLACENTAL TISSUE

| Starting material | Pretreatment | Extraction solvent | MBP recovery* |
|-------------------|--------------|--------------------|---------------|
| Fresh tissue      | None         | 0.15 M NaCl        | 9,310         |
| Fresh tissue      | (a) 0.1% collagenase digestion at 37°C for 18 h in PBS and (b) reduction and alkylation† | 0.15 M NaCl/0.01 M HCl | 17,378 |
| Freeze-thawed tissue | None         | 0.15 M NaCl        | 9,127         |
| Freeze-thawed tissue | Reduction and alkylation in 0.4 0.4 M NaHBO₃/NaH₂BO₃ | 0.15 M NaCl/0.01 M HCl | 13,429 |
| Freeze-thawed tissue | Reduction and alkylation in 0.4 M NaHBO₃/NaH₂BO₃ | 0.4 M NaHBO₃/NaH₂BO₃ | 14,797 |

* Recoveries are expressed as nanograms MBP per gram (wet weight) tissue, determined in the two-site immunoradiometric assay.
† Placental extracts were reduced in 0.0075 M dithiothreitol and they were incubated at room temperature for 60 min. Extracts were alkylated with iodoacetamide, final concentration 0.015 M, and they were incubated for 20 min at room temperature. See reference 13 for a complete discussion of the previously established need for reduction and alkylation in immunochemical detection of MBP.

Results

Localization of immunoreactive MBP by immunofluorescence. Fig. 1 shows the typical pattern of MBP immunofluorescence localization in term placentae. Immunofluorescence staining was limited to anchoring villi and was present at both cellular and extracellular sites; no tissue elements of absorptive villi, including syncytiotrophoblast, cytotrophoblast, Hofbauer cells, and fetal vasculature were stained. The cellular staining was confined to X cells, the large round cells found in anchoring villus and placental floor but not in absorptive villi. Higher magnifications show that only certain X cells have intense, diffuse cytoplasmic staining. Some X cells are less intensely stained, showing predominantly perinuclear speckling, and some do not stain at all. The extracellular substance showing such intense fluorescence is, when viewed by transmitted light in HE-stained sections, a palely eosinophilic, ground glass–appearing material, clearly...
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Figure 1. Immunofluorescence for MBP in delivered normal placenta. In this figure all panels are views of one tissue section, processed first for MBP immunofluorescence, photographed, and then counterstained with HE and again photographed. An exception to this is C, which is a section serial to that shown in the other panels, processed for immunofluorescence using normal rabbit IgG (instead of rabbit anti-MBP antibody) as a negative control. A is a low power view of placenta. The small islands of tissue are the absorptive villi (arrowheads), surrounded by the maternal blood space (b); in this section most of the blood has been washed out. The large central connective tissue structure (v) is an anchoring villus. B shows a higher magnification of the anchoring villus indicated by the box in A. The large round cells are X cells, the predominant cell type of the anchoring villus, and they are surrounded by a pale, ground glass–appearing substance. C is the serial section immunofluorescence-negative control.
distinguishable from maternal fibrinoid (20), which does not exhibit fluorescence. Fig. 2 shows the gathering of extracellular fluorescent material into a small lake, surrounded by palisades of X cells. This appears to be the microscopic counterpart of the macroscopic placental septal cyst.

Although affinity-purified antibody was used exclusively for the figures shown here, our initial experiments, which gave identical results, were made using whole rabbit antiserum to MBP. Tests of the specificity of this antiserum were carried out and the results are shown in Table III. Immunofluorescent staining of placenta was not altered by absorption with an unrelated basic protein, protamine, but was completely abolished by absorption with MBP-Sepharose. Further, neither preimmunization sera obtained from the same rabbit nor serum of another animal immunized with complete Freund’s adjuvant alone stained placenta.

In addition to these immunochemical tests of specificity, we determined whether immunofluorescent staining of placenta simply reflected the presence of maternal serum containing high levels of immunoreactive MBP. Maternal skin was resected at the time of cesarean section and was tested for immunofluorescence; no staining was found. Similarly, when maternal blood was clotted, formalin fixed, paraffin embedded, and stained for MBP, no staining was found except for the occasional brightly fluorescent peripheral blood eosinophil.

To determine whether all anchoring villi stained, sections cut from 17 blocks made from 8 normal placentae were examined. Of 34 anchoring villi identified on the HE-stained sections, 33 had MBP immunofluorescence (>97%). The
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**Table III**

*Immunohistochemical Specificity of Immunofluorescence*

| Reagent Description                                      | Adsorbent*            | Fluorescence Results |
|----------------------------------------------------------|-----------------------|----------------------|
| (a) Rabbit antihuman MBP antiserum                       | None                  | +                    |
|                                                          | Protamine-Sepharose†  | +                    |
|                                                          | MBP-Sepharose         | –                    |
| (b) Normal rabbit serum (preimmune serum)‡              | None                  | –                    |
| (c) Normal rabbit serum                                  | None                  | –                    |
| (d) Serum of rabbit treated with complete Freund’s adjuvant only | None                  | –                    |

* The preparation of these adsorbents is described in reference 15.
† Protamine was selected as a cationic protein with physicochemical qualities similar to those of MBP; macromolecular interactions based on charge rather than immunologic specificity would likely affect MBP and protamine to a similar extent.
‡ This was preimmunization serum obtained from the same animal from which the postimmunization specific antiserum tested in a was obtained.

Presence or absence of uterine labor had no effect on fluorescence, inasmuch as placentae obtained by elective cesarean section were indistinguishable from placentae delivered spontaneously.

Because initial immunofluorescence observations were made on third trimester–delivered placentae, we investigated placental MBP immunofluorescence during earlier stages of gestation. All 14 placentae examined from first and second trimester terminations of pregnancy (7 from each trimester) and a 6-wk spontaneous abortion showed both cytoplasmic and extracellular MBP immunofluorescence comparable to that shown in Figs. 1 and 2; the earliest placentae studied were obtained at 6 wk gestation.

The above results indicate that placental anchoring villi and certain of the X cells therein stain for MBP by immunofluorescence. Fig. 3 shows sections obtained from a postpartum hysterectomy where placental bed and decidual structures were found isolated by myometrium but in close proximity. The areas of deep adenomyosis contained only maternal decidual cells and did not stain, while the areas at the placental insertion site, containing X cells and placental-site giant cells, stained brightly. This observation was confirmed in another specimen by comparison of biopsies of decidua vera (endometrium from the uterine wall opposite the placental insertion site) and decidua basalis (endometrium at the placental insertion site). The decidua vera did not stain while the decidua basalis was strongly positive. These results suggest that MBP immunofluorescence is limited to trophoblastic and not maternal cellular elements at the choriodecidual junction.

Additional evidence favoring a trophoblastic origin for the immunofluorescence-containing cells was obtained from examinations of tissues from ectopic tubal gestations. Cellular immunofluorescence was observed in the conceptus of 10 of 13 tubal gestations, with some extracellular fluorescence in 2 of the 10 positive specimens. Hysterectomy was performed at the time of resection of two of the tubal gestations and the uterine decidual endometrial tissue had no MBP immunofluorescence, while the tubal conceptus, with no surrounding uterine
FIGURE 3. Immunofluorescence for MBP in a postpartum hysterectomy specimen. The patient from whom this tissue was obtained underwent a cornual resection for tubal gestation in the past. The present gestation was complicated by uterine atony in the third stage of labor, necessitating hysterectomy. All panels are views of one tissue section, processed first for immunofluorescence and subsequently counterstained with HE. A is a low power view showing endometrial epithelial cells and stroma implanted deep in myometrium (deep adenomyosis) as a consequence of the previous cornual resection. The endometrial elements have undergone the decidual changes of gestation. B is a higher magnification of the central area in A. C shows the complete absence of immunofluorescence in the identical field of deep adenomyosis framed in B. Panel D shows an area of the placental insertion site, at some distance from the area of deep adenomyosis. E and F (identical fields) show a higher magnification of the striking cytoplasmic immunofluorescence of the binucleate placental-site giant cells, located near the center of D. G and H (identical fields) are higher magnifications of the placental insertion site beyond the field of view in D and show that placental-site giant cells are associated with extracellular immunofluorescence. (A) × 25, (B–D) × 100, (E–H) × 400.
decidual cells, was positive for MBP immunofluorescence in both cases. Placentae from single cases of retained placenta, placental abruption, placenta accreta, and two cases of the pruritic urticarial plaques and papules of pregnancy syndrome all demonstrated specific immunofluorescence. Endometrial curettings from one case of chorioadenoma and three cases of hydatidiform mole showed cytoplasmic and extracellular fluorescence. One biopsy specimen of choriocarcinoma showed minimal cytoplasmic fluorescence and a second specimen had none. Endometrium from two premenopausal nongestational hysterectomy specimens, placenta from one case of anencephalic fetus, a normal fallopian tube, and a normal uterine cervix were all negative for specific immunofluorescence. Finally, umbilical cord did not show immunofluorescence. Examination of 20 methacrylate-embedded, Giemsa-stained sections of normal term placental tissue revealed no eosinophils other than the occasional typical peripheral blood eosinophil in a vascular space.

MBP in Tissue Extracts and Cyst Fluids. Because of the prevalence and intensity of the placental immunofluorescence findings, we attempted to solubilize placental MBP for comparison with MBP previously purified from the eosinophil granule. Dose-response curves for placental extract and purified MBP tested in the two-site immunoradiometric assay are shown in Fig. 4a. The curves are superimposable down to very low concentrations, where the placental extract shows greater anti-MBP antibody-binding activity. The dose-response curves for all five placental extracts shown in Table II were not statistically different from each other or the MBP standard, regardless of the extraction protocol used. Table II shows that the highest yield of MBP from placenta resulted from collagenase digestion, reduction and alkylation, and acidification.

Fig. 4b shows dose-response curves for purified MBP and placental cyst fluid.

![Figure 4](image-url)

**Figure 4.** Comparison of immunochromic reactivity of eosinophil granule MBP with material derived from placenta. Points plotted in a and b are arithmetic means of assay duplicates; duplicates did not vary >4%. (a) Dose-response curves for eosinophil granule MBP and placental extract in the two-site immunoradiometric assay. Placental extract No. 4 (see Table II) was tested here. Extracts prepared by any of the protocols in Table II gave dose-response curves that did not differ. (a) Granule MBP, (A) placental extract. (b) Dose-response curves for granule MBP and placental cyst fluid in the double antibody radioimmunoassay. (●) Granule MBP, (△) cyst fluid. Analysis of logit-log-transformed data revealed coefficients of determination for the MBP and cyst fluid regressions were 0.98 and 0.99, respectively. Though very similar, slopes for these lines were statistically different ($F_{1,15} = 4.9; 0.05 > P > 0.01$) by a one-way analysis of covariance.
as determined in the double antibody inhibition assay for MBP. From this assay, cyst fluid contained 100 μg MBP/ml, a sixfold increase above the highest maternal serum levels measured in gestation. When placental extracts were subjected to gel permeation chromatography on Sephadex G-50, all of the immunoreactivity was associated with the void volume species, as has been shown for the serum MBP molecule of gestation (13).

Discussion

The isolation of major basic protein from the eosinophil granule, its physicochemical properties, and its biological activities have been reviewed (3, 21). Human MBP is a relatively small arginine-rich protein, which in solution behaves as a polycation having an isoelectric point >10. MBP has at least two solvated sulfhydryl groups and it readily self-associates in concentrated solutions to form polymeric molecules. MBP is largely protein bound in physiological fluids, on the basis of both charge and disulfide linkages. When MBP is polymerized or covalently bound to other proteins, its recognition by a variety of specific antisera is inhibited (6, 19); for this reason, quantitative immunochemical measurement requires prior reduction and alkylation under nondenaturing conditions.

In the guinea pig, MBP is the sole constituent of the crystalloid core of the eosinophil granule (22). Human MBP is elevated in the serum of patients with eosinophilia, and the degree of elevation is correlated with the degree of eosinophilia (19) and with elevation of other eosinophil-related proteins such as Charcot-Leyden crystal protein (23). MBP is found in high concentrations in the sputum of patients with bronchial asthma (11) and has been demonstrated by immunofluorescence in the mucus plugs obstructing the bronchi of patients who have died with asthma (15). MBP provokes histamine release from basophils in a specific, noncytotoxic manner (12), but it is directly toxic to tracheal epithelium, other mammalian cells, and several helminths (3, 21). MBP has, therefore, been postulated as a mediator of the bronchial epithelial damage in asthma and of eosinophil-directed helminthocidal immune responses.

We have recently discovered that serum levels of immunoreactive MBP are elevated throughout human pregnancy (13). The degree of elevation correlates with the stage of gestation, with levels increasing from pre-gravid normals of <600 ng/ml to a plateau of ~7,500 ng/ml by the 20th wk of gestation. This elevation is comparable to the elevation of MBP seen in the serum of patients who have extreme degrees of peripheral blood eosinophilia, such as in the hypereosinophilic syndrome (19). Because cord serum MBP levels were normal, because maternal serum levels began to fall after delivery, and because we were unable to show any peripheral blood eosinophilia or elevation of other eosinophil-related proteins in serum of pregnant women with elevated serum levels of immunoreactive MBP, we postulated that the placenta is the source of this molecule. Here we show that immunoreactive MBP is localized in human placental tissue. The MBP localization is immunochemically specific, as shown by absorption experiments, and anatomically specific, as shown by its presence only in association with placental X cells and placental-site giant cells and its absence in maternal blood clot and nonreproductive maternal tissues. The cytotrophoblast and syncytiotrophoblast, which are the predominant cellular elements in placenta, are not associated with MBP immunofluorescence. It seems
unlikely that maternal endometrial decidual cells contribute to placental MBP immunofluorescence, because staining is seen in ectopic tubal pregnancy tissue where there are no maternal decidual cells present. Similarly, as shown in Fig. 3, the maternal decidual cells in the areas of deep adenomyosis, removed from the placental insertion site, are not associated with MBP immunofluorescence, while the adjacent areas from the same specimen, at the placental insertion site, stain positively for MBP in and around the placental-site giant cells.

MBP immunofluorescence appears to be present throughout normal gestation, because we found specific staining in placental tissue from terminations of normal gestation as early as 6 wk after conception. Although some specimens from early gestation had extracellular staining as well as cytoplasmic staining of X cells and placental-site giant cells, in general, the earlier the gestation the more likely cytoplasmic fluorescence predominated over extracellular fluorescence. The presence of MBP immunofluorescence was unaffected by the occurrence of uterine labor; placental specimens obtained by elective cesarean section were indistinguishable from those delivered after spontaneous parturition. This was also true when tissues from terminations of pregnancy (vacuum extraction without hormonal or pharmacologic interventions) were compared with tissues from spontaneous abortion.

We used the method of Godfrey et al. (17) to search for placental eosinophils because it offers two advantages over conventional histologic methods. Sections are thin enough to permit enumeration of single cells, and the tinctorial properties of mast cells, basophils, neutrophils, and eosinophils are the same as those usually obtained in peripheral blood, allowing unambiguous identification. In spite of these optimal conditions for observation, we were unable to demonstrate any tissue eosinophils in placental tissue in which abundant MBP immunofluorescence was found.

Quantitation of immunoreactive MBP in extracts of human placenta by both radioimmunoassay and immunoradiometric assay offers confirmatory evidence for the immunofluorescence findings. The observation that immunoreactive MBP concentrations in placental cyst fluid are more than six times higher than the highest levels measured in maternal serum discourages belief that MBP extracted from placenta is due solely to the content of maternal blood in the tissue. Localization of these very high concentrations of MBP to the placental cysts might be expected on the basis of our histologic and immunofluorescence finding and because prior observations have established the association of placental cysts with placental X cells, which are found lining the inner aspects of the cysts (24).

The limited physicochemical data available for the MBP molecule in placenta and maternal serum suggest some differences in comparison with MBP isolated from the eosinophil granule. In the immunoradiometric assay, dose-response curves for placental extracts and granule MBP are superimposable over most of the working range of the assay, except at very low concentrations where the placental extract actually has greater anti-MBP antibody binding activity than granule MBP. In the double antibody inhibition assay used to compare cyst fluid with purified granule MBP, cyst fluid MBP completely displaced granule MBP from specific antibody and the slope of the dose-response curve for cyst fluid MBP was greater than that for granule MBP. Finally, as has been shown for the
MBP in maternal serum (13), the MBP in placental extracts appears at the void volume of a Sephadex G-50 column instead of at the expected elution volume for monomer MBP isolated from the eosinophil granule. This latter observation suggests that the placental MBP molecule is larger than the eosinophil granule monomer MBP, and it is reasonable to speculate that the failure of perfect slope concordance in dose-response studies is somehow related to this apparent molecular size difference.

The precise origin of placental X cells and placental-site giant cells is controversial and their function is unknown. Placental X cells were first described by Scipiades and Burg (25), who noted their consistent location in placental septae, lining cystic structures, and in the basal decidual floor, where they are usually enmeshed in maternal fibrinoid, scattered among maternal decidual cells. Ultrastructural studies have shown that these cells possess a microvillus surface, well-developed Golgi apparatus, and extensive rough endoplasmic reticulum, suggesting very active protein biosynthetic activity (26). Autoradiography using tritiated thymidine has revealed DNA synthesis in a substantial portion of these cells (24), and immunofluorescence examinations for human chorionic gonadotrophin have been negative (27). An association between severe abnormal proliferation of X cells and fetal intrauterine growth retardation has been reported (28). In contrast, much less is known about the placental-site giant cell. This cell is found only in relation to maternal endometrial and myometrial cells at the placental insertion site. Immunofluorescence for human chorionic gonadotrophin in these cells has been reported positive and, using quinacrine fluorescence (for F bodies) in male gestations, a trophoblastic origin for placental-site giant cells has been reported (27).

The immunofluorescence findings in this paper provide some immunochemical evidence to suggest that the X cells and the placental-site giant cell may be functionally related specialized derivatives of trophoblast. The placental-site giant cell has been postulated to play a key role in establishing the invasiveness of the trophoblastic mass at the time of implantation, and it is tempting to speculate that MBP, a cytotoxic molecule as isolated from the eosinophil, might be synthesized by such an invasive cell to mediate maternal decidual cell necrosis and enhance implantation. This hypothesis fails to account for continued production of MBP throughout gestation, however, and leaves unaddressed the function of MBP produced by the placental X cell.

Summary

We have recently reported that human pregnancy is characterized by a 10- to 20-fold elevation of eosinophil major basic protein (MBP) immunoreactivity in maternal blood. Here we show, by immunofluorescence, that placental tissue specifically binds antibody to MBP in and around the placental X cells and placental-site giant cells and, using thin plastic sections, that placenta has no infiltrating eosinophils. The X cells line the inner aspects of placental septal cysts, and the cyst fluid, obtained by aspiration, contains immunoreactive MBP at concentrations of 100 µg/ml, a sixfold greater concentration than the highest levels measured in maternal blood.

The soluble MBP immunoreactivities in placental homogenates and in maternal serum chromatograph identically on Sephadex G-50, and both these gesta-
tional MBP molecules migrate as though substantially larger than the MBP found in serum from patients with hypereosinophilic syndrome or purified from the eosinophil granule. Our inability to demonstrate eosinophils in maternal blood or placental tissue, coupled with the large quantities of immunoreactive MBP highly localized in placental cysts and the chromatographic behavior of this molecule, suggest that the MBP detected in human gestation is produced by placenta.

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