Infantile Hemangiomas
Speculation on Placental Trophoblastic Origin
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Background: The unique immunobiology of the placental trophoblast and the increased incidence of hemangiomas in infants born after chorionic villus sampling suggest that an immunologically regulated ectopic focus of trophoblasts could be the cell of origin for proliferative infantile hemangiomas.

Objective: To compare tissue from infantile hemangiomas with that of other vascular lesions for the presence of selected placental trophoblast-specific cellular markers.

Design and Patients: Twelve tissue specimens taken from infantile hemangiomas on patients aged 5 days to 2 years were retrospectively confirmed clinically and histologically. Negative controls were similarly confirmed, including 6 pyogenic granulomas and 4 vascular-lymphatic malformations. These tissues were used for immunohistochemical analysis of selected trophoblastic markers including human placental lactogen, placental alkaline phosphatase, and cytokeratins 7, 8, and 17.

Setting: Tissue submitted from patients seen at Saint Louis University Department of Dermatology and Cardinal Glennon Children’s Hospital in St Louis, Mo, between January 1, 1997, and October 31, 1999.

Main Outcome Measure: Differential staining for trophoblastic markers in infantile hemangiomas compared with control tissues.

Results: The 12 infantile hemangiomas were uniformly negative for all markers tested. Control tissues were also negative for these markers. Four of the 5 histochemical markers did recognize specific nonvascular, cutaneous elements: placental alkaline phosphatase stained smooth and striated muscle, cytokeratins 7 and 8 stained eccrine glands, and cytokeratin 17 stained pilosebaceous units.

Conclusions: Our results do not support the placental trophoblast as the cell of origin for infantile hemangiomas, but we hope our observations and speculation will stimulate further study of this hypothesis.

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EMANGIOMAS are the most common tumor of infancy, with an estimated incidence of up to 12%, most often occurring in whites, females, and premature infants weighing less than 1000 g.1-3 Chorionic villus sampling (CVS) is an underappreciated predisposing factor. One study reported that 21% of 432 CVS-exposed infants developed hemangiomas. In one third of the cases, the lesions were multiple.4,5

The pathogenesis of this tumor has remained elusive. Insights historically have been obscured by ambiguous and inconsistent nosologic systems. Mulliken and Glowacki’s6,7 breakthrough in the classification system of vascular birthmarks provided direction based on clinical and cellular features. Recent investigation has concentrated on angiogenesis as a possible pathogenic mechanism. Developmental cellular interactions with an associated imbalance of angiogenic and antiangiogenic factors have been postulated to trigger an abnormal endothelial cell proliferation.8-10 Other studies have focused on the role of interactions between resident mast cells and fibroblasts7,17 as well as differential expression of a variety of growth factors during hemangioma proliferation and involution.18 Some of these factors also play a role in placental physiology (Table).

Decades before the investigations into angiogenesis, a developmental embryonic origin of hemangiomas was posulated by several authors7,22 and deserves further examination. The placenta is a complex barrier that affords the embryo immunologically privileged growth.19,23
PATIENTS AND METHODS

Pathological specimens given the histologic diagnosis of hemangiomma between January 1, 1997, and October 31, 1999, at Cardinal Glennon Children’s Hospital in St Louis, Mo, were reviewed, along with clinically and histologically consistent cases of infantile hemangiomas diagnosed at St Louis University Department of Dermatology. Twelve samples were categorized as infantile hemangiomas by the histologic presence of endothelial proliferation and a consistent clinical history of postnatal disproportionate growth and eventual spontaneous resolution. The 14 negative controls included 10 pyogenic granulomas and 4 vascular-lymphatic malformations characterized by typical clinical history and consistent histologic findings. Positive controls were randomly selected normal placentas sectioned through the chorionic vili.

The tissues were all embedded in paraffin and cut at 4 µm. The sections were stained with routine immunohistochemistry techniques that used monoclonal antibodies to cytokeratin 7 (clone OVTL 12/30; Dako Corp, Carpenteria, Calif), cytokeratin 8 (low-molecular-weight keratin, clone 35BH11; Dako Corp), cytokeratin 17 (clone E3; Dako Corp), placental alkaline phosphatase (clone 8A9; Dako Corp), and polyclonal rabbit anti-human placental lactogen (lot 054; Dako Corp).

Slides were reviewed by a pediatric pathologist (C.S-A.), a dermatologist (E.S.), and a dermatopathologist (G.N.) to assess for the presence or absence of positive staining for each trophoblastic marker.

The cellular immune interaction between fetus and mother is a current focus of intense research interest. The trophoblast is a highly proliferative stem cell at the maternal-fetal junction. Invasive functions allow trophoblasts to initiate and establish maternal-fetal circulation by eroding the uterine mucosa, engulfing maternal spiral arteries, and eventually replacing arterial smooth muscle and lining the maternal-fetal intervillous space as a modified type of endothelial cell. Differentiated trophoblasts then mature to become the functional units of the placenta: absorbing oxygen and nutrients, producing steroid and protein hormones, and preventing fetal alloimmunization. The complex physiologic activity of the trophoblast is mirrored by its complex evolution into multiple cell types with expression of varying cellular and immunologic markers.

The direct contact of maternal and fetal cells at the placental interface allows admixture of not only oxygen and nutrients, but also cells. Fetal cells entering the maternal circulation have been associated with a variety of adverse sequelae. The transfer of fetal red blood cells causes Rh isoimmunization. Trophoblasts can be identified in maternal peripheral blood, along with antitrophoblast antibodies that have been implicated as a cause of recurrent spontaneous abortion. The migration of fetal cells into maternal skin have been implicated as a cause of polymorphic eruptions of pregnancy and are one presumed cause of the chronic graft-vs-host reaction, which manifests as systemic sclerosis in women. Conversely, maternal cells may enter the fetal circulation and lead to in utero graft-vs-host disease as well as metastatic malignant neoplasms.

The admixture of maternal and fetal cells, common to all pregnancies, is enhanced by placental trauma.

### Differential Expression of Growth Factors and Receptors in Placenta and Hemangiomas

<table>
<thead>
<tr>
<th>Growth Factors</th>
<th>Maternal Placenta</th>
<th>Fetal Placenta</th>
<th>Hemangioma</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCNA</td>
<td>Negative</td>
<td>Invasive extravillus trophoblast, cytotrophoblast shell, cytotrophoblast nuclei: early term &gt;midterm &gt;full term</td>
<td>Proliferative &gt;&gt; involuting</td>
</tr>
<tr>
<td>VEGF</td>
<td>Maternal endothelium, all stromal cells, endothelium of villus stroma adjacent to trophoblast proliferation</td>
<td>Cytotrophoblasts lining extraembryonic cavity, cytotrophoblasts lining villi, forming columns and anchoring villi</td>
<td>Proliferative &gt;&gt; involuting</td>
</tr>
<tr>
<td>MMP/type IV collagenase</td>
<td>Stromal villus especially in first trimester, increased with labor, glandular structures</td>
<td>Cytotrophoblast cell column, choriodicuda, amniotic fluid</td>
<td>Proliferative &gt;&gt; involuting</td>
</tr>
<tr>
<td>bFGF</td>
<td>Endometrial cells, mesometrial decidua</td>
<td>Receptors on blastocyst, secreted by trophoblast, increased in fetal/neonatal serum</td>
<td>Proliferative &gt;&gt; involuting &gt;&gt; involuted</td>
</tr>
<tr>
<td>Urokinase</td>
<td>Decidual cells</td>
<td>Vitellus trophoblast, proliferative and invasive cytotrophoblast, extravillous trophoblasts associated with uterine arterioles</td>
<td>Proliferative &gt;&gt; involuting &gt;&gt; involuted</td>
</tr>
<tr>
<td>TIMP</td>
<td>Constant throughout gestation, decreased with labor</td>
<td>Cultured human cytotrophoblasts, syncytiotrophoblasts, amniotic fluid</td>
<td>Involuted &gt;&gt; involuted</td>
</tr>
<tr>
<td>vWF</td>
<td>Maternal endothelium</td>
<td>Human umbilical cord artery and vein, endothelial cells of villus microvessels</td>
<td>Proliferative = involuting &gt;&gt; involuted</td>
</tr>
</tbody>
</table>

* Data from Beer and Sio, Blankship and King, and Kim et al. PCNA indicates proliferating cell nuclear antigen; VEGF, vascular endothelial growth factor; MMP, metalloproteinase; bFGF, basic fibroblast growth factor; TIMP, tissue inhibitor metalloproteinase; vWF, von Willebrand factor; =, equal expression; >, stronger expression; and >>, much stronger expression.
Rh(D) immune globulin is routinely administered to pregnant, Rh-negative women before amniocentesis or after motor vehicle accidents to prevent isoimmunization. Inflicted placental trauma and CVS result in hemorrhagic lesions that can be seen on the embryo. In addition, CVS is associated with a 3-fold increase in hemangiomas, compared with amniocentesis.

With these observations in mind, this study was designed to look for evidence of cellular trophoblastic markers in tissue taken from infantile hemangiomas to establish a link between these tumors and placental trophoblasts.

RESULTS

Tumor cells from the 12 samples of clinically and histopathologically consistent hemangiomas were uniformly negative for cytokeratins 7, 8, and 17; placental alkaline phosphatase; and human placental lactogen, as was pathological tissue from all negative controls, including 12 cases of pyogenic granulomas and 4 cases of arteriolymphatic malformations. Trophoblasts within the 2 placental samples stained for all markers. Of note, 4 monoclonal antibodies did recognize specific nonvascular, cutaneous elements: antibodies against placental alkaline phosphatase stained smooth and striated muscle (Figure 1), cytokeratin 17 stained pilosebaceous units (Figure 2), and cytokeratins 7 and 8 stained eccrine glands (Figure 3). Antibody staining for human placental lactogen was negative.

COMMENT

Our results neither supported nor excluded the concept of a trophoblastic origin for infantile hemangiomas. The complex nature of the stem cells known as trophoblasts make histochemical identification technically challenging. We selected commercially available immunostains relatively specific for undifferentiated trophoblasts. Human placental lactogen is known to be secreted by trophoblasts into maternal serum throughout pregnancy, whereas placental alkaline phosphatase is secreted during the second and third trimesters. Cyto-keratins 7, 8, and 17 have been identified as specific markers of trophoblast subpopulations within the chorionic villi. In comparison, a recent abstract reported 37 juvenile hemangiomas that immunostained with monoclonal antibodies against microvascular markers uniquely coexpressed in the more well-differentiated placental microvasculature, rather than trophoblast stem cells. These markers included merosin, GLUT-1 (glucose transporter isoform 1), Lewis Y, and FcγRII (a placental endothelial antigen), which failed to react in all 25 vascular malformations.
Our findings did not support our hypothesis, but a placental origin of hemangiomas is consistent with several well-described interactions between placenta, fetus, and mother. Our hypothesis also fits several epidemiologic and clinical features of infantile hemangiomas.

The trophoblast has many properties that could permit the development of hemangiomas. It is a stem cell with a profound and varied functional capacity. Its potential for initial invasion and subsequent implantation and proliferation makes it possible that this cell is under the same regulation as other placental endothelial cells and could be affected by angiogenic and antiangiogenic factors. The complex immunobiology of placental interactions with the presence of HLA markers and complement regulatory proteins on the trophoblastic cell surface provides evidence of this cell’s unique immunologic activity, its immune-privileged status, and its strategies to protect itself.20,23,24

Clinical and epidemiologic observations also support a placental origin for infantile hemangiomas. Premature infants have a higher incidence of hemangiomas. This may be related to a relative immunologic naïveté or a decrease in maternal antibody levels (including antitrophoblast antibodies), since the initial transfer of maternal IgG occurs at 20 weeks’ gestation and the majority of transfer, after 32 weeks’ gestation.29,42 The preponderance in female infants may be explained by a relative immunologic tolerance related to cyclic angiogenesis during menstruation, ovulation, and future pregnancies.43 The natural course could also be the result of immunologic responses. Postnatal proliferation is typical in these tumors and may be coincident with waning maternal IgG, including antitrophoblast antibodies (with a half-life of 25 days and nadir at 3-4 months postnatally).42 The approximate growth phase is 9 months, as is the growth phase of the placenta. The eventual involution of hemangiomas could represent a process related to preprogrammed placental apoptosis known to increase throughout gestation.45-48

Our theory was inspired by the unexplained observation that hemangiomas are the most common anomaly associated with CVS.4,5,49 All pregnancies are at risk for cell admixture at the placental interface, even without overt trauma; however, the nature of CVS disrupts chorionic villus trophoblasts and could easily allow dissemination into the fetal circulation or amniotic fluid. Among a group of 14 CVS-exposed infants with limb disruption defects, 50% had 1 or more hemangiomas.5 Both sporadic and CVS-associated hemangiomas occur most often on the head and neck, representing 60% of fetal surface area available for implantation.1 Hemangiomas can also occur in strikingly typical patterns and locations. Ectopic implantation of placental trophoblasts could account for these characteristic distribution patterns, depending on the stage of embryonic development at implantation. Segmental or midline hemangiomas could develop after early implantation, along with the developing branching arches of the head and neck. Late transamniotic implantation could result in local lesions, while late hematogenous spread could result in disseminated cutaneous and visceral lesions.

Although speculative at present, the theory seems to explain many unknowns in regard to this most common and little understood tumor of infancy. Additional studies as to a placental origin of hemangiomas may provide more useful information and may eventually lead to a more specific, possibly immunologic treatment to prevent development of this neoplasm and its serious complications, including ulceration, pain, obstruction, and disfigurement.30

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REFERENCES