Fetal Antigens in Nonneoplastic Conditions

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Summary

During studies that showed the presence of fetal antigens on the surface of human malignant melanoma tumor cells, polyvalent antisera specific for human fetal tissues of varying ages were developed. These reagents demonstrated varying patterns of expression of fetal antigens at different ages in various tissues of the human fetus. The possibility that nonneoplastic adult cells showing either maturation arrest or excessive proliferation also might express fetal antigens led to studies of human bone marrow. Although normal bone marrow cells expressed low levels of fetal antigens, large amounts were seen on bone marrow cells of patients with anemias due to iron, B12, or folic acid deficiencies, as well as on those with leukemia. Moreover, normal adult tissues adapted to long-term culture also expressed fetal antigens. After 3 weeks in organ culture adult human skin showed morphological changes similar to those seen in fetal periderm and strongly expressed fetal antigens. In addition, lymphoblasts in long-term cultured human lymphoid cell lines established from normal donors also carried surface fetal antigens. These latter antigens were shared with neoplastic B-cells (chronic lymphocytic leukemia) but not with T-cells. Their expression varied with the cell cycle. The reexpression of fetal antigens on malignant cells is thought to signal a basic derangement in the control of cell maturation and proliferation in adult tissues. Moreover, normal adult cells also may reexpress fetal antigens under circumstances unrelated to neoplasia but associated with either maturation arrest or rapid and excessive proliferation.

Introduction

Fetal substances, designated "antigens" since they are detected immunologically, are frequently reexpressed during neoplasia. Carcinoembryonic antigen, α-fetoprotein, sulfoglycoprotein, fetal ferroprotein, γ-fetoprotein, and T-globulin have each been reported in certain types of cancer (6). Although initially regarded as characteristic of neoplastic states, it is now known that these substances may be present in small amounts in normal adult tissues and may be reexpressed in nonneoplastic conditions as well. Simple cell proliferation is an attractive explanation for the basis of fetal antigen expression, such as the production of α-fetoprotein in some patients with nodular regeneration of the liver (42) or in rats after carbon tetrachloride-induced hepatic injury (3).

Certain types of increased cellular activity in the adult that are akin to those occurring during fetal development may be important. The bursts of cellular activity that accompany tissue and organ development during fetal life exhibit many of the features of hyperplasia and cancer, including migration of cells and movement of tissues, in addition to rapid growth. Thus, fetal substances, especially those expressed on cell surfaces at varying points during fetal life, may play a very fundamental role in the regulation of the intricate patterns of fetal development. From this point of view fetal antigen expression in neoplasia would accompany the disordered processes of differentiation characteristic of the malignant state.

It seemed reasonable, therefore, to look for the presence of fetal substances in nonneoplastic conditions where cells and tissues produce bursts of cellular activity or show defective maturation. This paper summarizes investigations on the expression of fetal antigens on bone marrow cells, on skin undergoing long-term culture, and on lymphoid cells in man. Evidence is presented to link the expression of fetal antigens to the regulation of cell maturation and proliferation in adult tissues.

Fetal Antigens on Human Melanoma Cells

The initial studies began with human malignant melanoma. A number of distinct tumor-associated antigens have been described (21, 22), including a cell membrane individually specific antigen and a cross-reactive cytoplasmic antigen. Attempts were made to see whether the cytoplasmic antigen might be fetal in type, thus accounting for its cross-reactivity (1).

Polyvalent antisera were deliberately prepared for this purpose. Human fetuses were obtained through therapeutic abortions at 12 to 16 weeks of age as judged by crown to rump measurements. Glycoproteins were then prepared by perchloric acid extraction. After removal of the brain, spinal cord, and internal organs, the remaining corpus was homogenized with 2 volumes of water in a Virtis blender. The homogenate was then extracted ultrasonically for three 1-min intervals, and an equal volume of 0.8 M perchloric acid was added. After centrifugation, the supernatant was dialyzed against running tap water overnight (5°). The precipitate that formed was dissolved in a Tris-glycine-EDTA buffer, pH 8, at a final concentration of 0.1 M Tris, 0.3 M

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1 Presented at the Symposium "Cancer and Chemistry" as part of the Fourth Conference on Embryonic and Fetal Antigens in Cancer, November 2 to 5, 1975, Charleston, S. C. Research supported by National Cancer Institute and Medical Research Council of Canada.

2 Presenter. Scholar of the Medical Research Council of Canada. To whom requests for reprints should be addressed, at McGill University Cancer Research Unit, McIntyre Medical Sciences Building, 3655 Drummond Street, Montreal, Quebec, Canada H3G 1Y6.
glycine, 0.001 M EDTA, and 0.2 M NaCl. The solution was concentrated by ultrafiltration through an Amicon PM-10 membrane and stored at −20° until used.

The antisera were prepared in New Zealand White rabbits. Each animal received intradermal injections in multiple sites containing a total of 2 mg of antigen mixed with an equal volume of complete Freund's adjuvant. One month later each animal received a 2nd dose of antigen in incomplete Freund's adjuvant injected i.m. The rabbits were bled 10 days after the last injection. Antibodies to normal serum components were removed by absorption with a gel prepared from a pool of human sera treated with glutaraldehyde (2). Reactivity with adult tissues was removed by sequential absorptions with acetone powders of adult liver, spleen, muscle, and brain. Absorptions with fetal calf serum did not alter subsequent results. The absorbed antisera were evaluated by indirect immunofluorescence on frozen sections of fetal tissues. The final antisera did not react with adult tissues, but widespread reactivity remained against fetal cells of the gut, liver, kidney, muscle, and adrenal but not the brain.

With these polyvalent antifetal sera, a number of human tumors were examined by direct and indirect immunofluorescence against viable cells and snap-frozen smears. Results were positive with cells of malignant melanoma and tumors of the colon, breast, and kidney (1). Two teratomas, 1 neuroblastoma, and 2 Wilms' tumors gave positive results as well. Extracts of fetal and melanoma cells also reacted in immunodiffusion plates. In the case of melanoma both surface membrane and cytoplasmic fetal antigens were detected. Immune blocking and absorption experiments confirmed the specificity of the antifetal sera and showed that the melanoma-specific membrane and cytoplasmic antigens were distinct and different from the fetal antigens (36).

Age- and Tissue-specific Fetal Antigens

In early studies with these polyvalent antisera, it was noticed that an antiserum raised against a parchloric acid extract of human fetus in which brain and spinal cord were excluded showed reactivity against tissues and tumors of nonbrain origin but failed to cross-react with fetal or normal adult brain or with a series of brain tumors. Moreover, when a fetus 20 weeks old instead of 10 weeks was used as a source of antigen, the resulting antisera no longer had the same fetal specificity and they cross-reacted with a number of adult cell types. Thus, studies of this kind must allow for age- and tissue-specific variation in the expression of fetal antigens.

The primitive neural tube in the human embryo is closed off from contact with other fetal tissues by the end of the 4th week of development (20). The central nervous system is thus sequestered from the immune system very early in fetal development. It seemed appropriate, therefore, to obtain antisera to fetal central nervous system components (designated “brain”) and to compare these at different time intervals ranging from 10 to 17 weeks with antisera raised against tissues from the rest of the fetus (designated “corpus”) (R. Pitzele and M. G. Lewis, manuscript in preparation). For this study antifetal sera were produced against 10-, 12-, 14-, 16-, and 17-week corpus tissues and against 14- and 17-week brain and were absorbed with acetone powders of adult spleen, liver, muscle, skin, and brain tissues as described previously. The analysis was carried out by indirect immunofluorescence on frozen sections of fetal tissues. Depending on the antisera used, antigens were found on all neural elements of the brain and spinal cord; the epidermal and follicular cells of the skin; striated, smooth, and cardiac muscle; the epithelial lining cells of the lung; the crypt and villus lining cells, serosal mesothelial cells, and elements of the lamina propria of the intestine; the parenchymal cells of the liver; and the cells of the renal tubules and glomeruli. Fetal spleen, thymus, and thyroid were negative with the anticorpus sera and gave only nuclear reactions with the antibrain sera. Connective tissues did not react with either type of antisera.

The data summarized in Table 1 show striking differences in the expression of fetal antigens in nervous and muscle tissues. Examples of major age differences in the expression of fetal antigens also are shown for skin and liver. Besides providing additional evidence for the phasic and tissue-specific nature of fetal gene expression during development, these studies emphasize the importance of controlling for such variability in the preparation of fetal antigens and antisera for use in studying various tumor types. The detailed studies with this battery of antifetal sera now in progress are establishing the time and tissue sequences for the expression during fetal development of various gene products that may be reexpressed in different tumor types.

Fetal Antigen Expression in Cultured Explants of Adult Human Skin

Characteristic degenerative and regenerative changes occur in cultured skin (34, 36), and the epidermal cells display a primitive, fetal-like appearance. The polyvalent antifetal sera were used to see whether the dedifferentiation occurring in long-term cultured skin led to the production or reexpression of fetal gene products on the surfaces of cells.

In double-blind experiments full-thickness skin grafts kept in culture from 9 days to 18 weeks were examined by immunofluorescence and electron microscopy (23) (Table 2). The skin showed positive immunofluorescence, either in large primitive-looking cells remaining attached to the basement membrane or in the area between the exuberant stratum corneum that forms under these conditions and the remaining attenuated epidermis. Normal noncultured adult skin was negative; fetal skin was strongly positive, as expected, and an intermediate effect was seen in the skin from the foreskin of the 1-day-old child. Experiments with cell suspensions were corroborative, and electron microscopic studies confirmed the fluorescence results in addition to locating the fetal antigens in the intercellular space between cells of the granular and cornified layers, as well as on the surfaces of cells in the basal layer. Thus, under adverse conditions of in vitro growth, adult skin after 3 weeks in culture not only degenerates markedly but also regenerates. Under these circumstances primitive-looking cells appear in the epidermis that resemble cells of the fetal
Age and tissue-specific variation in human fetal antigen expression

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Antifetal corpus</th>
<th>Antifetal brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Nervous tissue</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Ependyma</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Striated muscle</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Smooth muscle</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cardiac muscle</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major age differences</th>
<th>Age of fetal tissue</th>
<th>Age of antifetal tissue</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.5- and 17-wk skin</td>
<td>14- and 16-wk antifetal corpus</td>
<td>hair follicles +</td>
<td></td>
</tr>
<tr>
<td>16-wk and 5-mo. skin</td>
<td>16- and 17-wk antifetal corpus</td>
<td>hair follicles –</td>
<td></td>
</tr>
<tr>
<td>5-mo. skin</td>
<td>12-wk antifetal corpus</td>
<td>epidermis –</td>
<td></td>
</tr>
<tr>
<td>5-mo. skin</td>
<td>14-, 16-, and 17-wk antifetal corpus</td>
<td>epidermis +</td>
<td></td>
</tr>
<tr>
<td>6-wk liver</td>
<td>10-wk antifetal corpus</td>
<td>hepatocytes +</td>
<td></td>
</tr>
<tr>
<td>6-wk liver</td>
<td>17-wk antifetal corpus</td>
<td>hepatocytes –</td>
<td></td>
</tr>
</tbody>
</table>

Fetal antigens on cultured adult human skin

<table>
<thead>
<tr>
<th>Tissue sections</th>
<th>Intensity of immunofluorescence</th>
<th>Cell suspensions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in culture</td>
<td>Membrane immunofluorescence</td>
<td>Cytoplasmic immunofluorescence</td>
</tr>
<tr>
<td>4 days</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>1 wk</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>2 wk</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>3 wk</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>6 wk</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>11 wk</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>16 wk</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

periderm and that express surface fetal antigens.

One possible explanation for the extended survival of long-term cultured human skin on allogeneic transplantation might involve the expression of fetal antigens on the surface of the newly formed epidermis. Masking or interference with the expression of the normal HLA antigens known to be still present in the transplant may be involved. Early reports (16, 17, 40, 41) suggesting that skin allograft survival could be enhanced by the cultivation of tissue in organ culture before transplantation have been severely criticized, and some attempts to repeat them have failed (19, 31, 44). However, Janssen de Limpens et al. (18) have recently reported that an allogeneic 2nd-set reaction could be temporarily weakened in white Swiss mice by culturing the skin graft in vitro for at least 6 weeks before grafting. Moreover, in rats, Heslop et al. (12, 13) have shown that fetal skin usually survives longer than the equivalent adult skin, especially under conditions of weak incompatibility. The survival time of skin grafts becomes progressively shorter between birth and old age. As in mice (37, 45), the grafting of neonatal skin in rats causes considerable prolongation of the survival time of simultaneously grafted skin from adult donors (12, 13). Some of the difficulty with skin graft experiments has been attributed to failure of the graft to revascularize before becoming dehydrated (19). In this regard recent reports have appeared showing that the survival of the thyroid (19) and ovarian allografts (15, 25) is also enhanced after organ culture of the transplanted tissue. Opelz and Terasaki (33) have demonstrated that during culturing for more than 4 days human PBL3 lose their ability to stimulate allogeneic lymphocytes in mixed lymphocyte cultures, but they retain their ability to respond to allogeneic lymphocytes or to phytohemagglutinin for up to 10 days. The numbers and specificities of the HLA antigens remain unchanged. If the loss of immunogenicity of cultured skin can result from an effect on passenger lymphocytes, these findings could account for the transplantability of cultured skin. On the other hand, our demonstration of fetal antigens on cultured B-lymphoblasts (see below) may be relevant to this situation also.

Fetal Antigens in Human Bone Marrow Cells

Another example of a tissue capable of bursts of cellular activity and easily accessible for study is the bone marrow. Rabbit antisera to 12-week-old human fetal tissues were used to identify cells in human bone marrow that might be expressing fetal substances under a number of different conditions such as B12 deficiency, iron deficiency, or leukemia (24). For these experiments a comparator microscope system (11) was used to quantitate fluorescence intensity in addition to the usual direct and indirect immunofluorescence assays on snap-frozen marrow smears.

The results summarized in Table 3 show that both non-neoplastic and neoplastic conditions in which marked marrow hyperplasia occurs are associated with fetal antigen expression. In these studies the majority of normal bone marrow preparations showed less than 20% cells fluorescing (2 to 15%) with weak intensity below 5 on the comparator microscope system (11) was used to quantitate fluorescence intensity in addition to the usual direct and indirect immunofluorescence assays on snap-frozen marrow smears.

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Thus, in situations in which some form of abnormal but nonneoplastic cellular development or proliferation is occurring, bone marrow cells express fetal substances. The phenomenon is most striking under those conditions where some form of maturation arrest and abnormal cell growth occur, as, for example, in B₁₂ and folic acid deficiency and to a lesser extent in iron deficiency. In fact, one of the conditions for which false-positive carcinoembryonic antigen has been reported is pernicious anemia (10). The specificities of the antifetal sera used in this study are under investigation. It is known that the antiserum cross-react with both carcinoembryonic antigen and α-fetoprotein but that they recognize additional antigens as well.

**Fetal Antigens on Human B Lymphoid Cells**

Although the expression of fetal antigens on leukemia cells is not particularly surprising, the results with the bone marrow experiments in nonneoplastic conditions led to studies of lymphoid cells. When normal constraints upon growth are absent, then the presence of fetal proteins may be anticipated. Lymphoblastoid cell lines established from normal individuals grow in suspension and maintain some differentiated characteristics. They provide, therefore, unusual opportunities to study such adaptive changes.

Using the polyvalent antifetal sera in indirect immunofluorescence, B-lymphoblast lines were found to carry surface membrane fetal antigens (39), with 44 to 74% of the cells reacting (Table 4). These lines were established in long-term culture from normal human donors. Experiments with a sensitive isotopic antiglobulin assay were confirmatory (38). By electron microscopy, immunoperoxidase techniques combined with specific immune blocking experiments established both the specificity of the antifetal sera and the surface location of the antigens. Antisera to fetuses ranging in age from 8 to 17 weeks were examined, and only those against 9- to 10-week extracts gave significant reactions. This selective expression of fetal antigens at different gestational ages accords with the earlier studies with these reagents cited above.

The MOLT-4 line, in contrast, gave no significant reaction. This line was derived from a patient with acute lymphocytic leukemia and expressed T-cell characteristics (28). However, in our hands this line has largely lost its capacity to form significant numbers of T- and complement rosettes, so that its failure to display fetal antigens may represent artifactual dedifferentiation in culture. Human thymocytes also failed to express these fetal antigens, suggesting that they might characterize B-lymphoid cells.

In agreement with this suggestion, circulating tumor cells from 3 patients with CLL also carried large amounts of fetal antigens, as did the Burkitt lymphoma line Daudi. Ten- and 12-week antigens could also be detected in small amounts circulating in the sera of 2 CLL patients by precipitin analysis in Ouchterlony plates.

Ficoll-Hypaque-isolated PBL obtained from 17 normal donors showed a low level of reactivity [19 ± 8% (S.D.)] (39). These figures correlated closely with normal B-cell levels. Absorption experiments then suggested cross-reactions between cultured lymphoblasts and normal PBL. Nylon wool columns were then used to remove adherent B-cells and monocytes from the PBL populations. This procedure markedly decreased immunoglobulin-bearing B-cells as measured by immunofluorescence and enriched rosetting T-cells. Cells bearing fetal antigens were also depleted by this manipulation, but the reduction was variable and less than that of B-cells. These preliminary experiments seem to indicate that a subpopulation of normal PBL shares reactivity with the antifetal sera with cultured lymphoblasts. It is quite possible that an immature precursor subpopulation of normal PBL might temporarily express lymphocyte fetal antigens, such as, for example, the small subpopulation bearing mixed membrane markers (4). Studies of patients with immune deficiency disorders may be helpful in sorting out whether these antifetal sera can detect developmental

### Table 3

**Fetal Antigens on Human Bone Marrow Cells**

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of patients with condition</th>
<th>No. of patients positive</th>
<th>Cells fluorescing (%)</th>
<th>Comparator reading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>20</td>
<td>4 (20%)*</td>
<td>14.1 ± 9.7*</td>
<td>4.5 ± 1.6</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>21</td>
<td>12 (57)</td>
<td>29.9 ± 14.2</td>
<td>7.3 ± 2.9</td>
</tr>
<tr>
<td>B₁₂ deficiency</td>
<td>31</td>
<td>23 (74)</td>
<td>49.9 ± 19.7</td>
<td>10.4 ± 4.3</td>
</tr>
<tr>
<td>Leukemia</td>
<td>38</td>
<td>31 (82)</td>
<td>49.6 ± 21.3</td>
<td>10.4 ± 4.2</td>
</tr>
<tr>
<td>Erythroid hyperplasia</td>
<td>6</td>
<td>5 (83)</td>
<td>39.3 ± 13.7</td>
<td>8.3 ± 4.4</td>
</tr>
</tbody>
</table>

* Determined by immunofluorescence.  
* Fluorescence intensity in comparator units (mean ± S.E.) measured by comparator microscope.  
* Numbers in parentheses, percentages.  
* Mean ± S.D.

### Table 4

**Fetal Antigens in Nonneoplastic Conditions**

<table>
<thead>
<tr>
<th>Test system</th>
<th>Membrane immunofluorescence with anti-10-wk fetal sera (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cultured lymphoblasts</td>
<td>62 ± 10*</td>
</tr>
<tr>
<td>B line (5 tested)</td>
<td></td>
</tr>
<tr>
<td>T line (1 tested)</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Daudi (Burkitt lymphoma)</td>
<td>82 ± 4</td>
</tr>
<tr>
<td>CLL (N = 3)</td>
<td>66 ± 10</td>
</tr>
<tr>
<td>Normal thymus (N = 3)</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Normal PBL (N = 17)</td>
<td>19 ± 8</td>
</tr>
</tbody>
</table>

* Results obtained with 3 separated rabbit antisera.  
* Mean ± S.D.
antigens on immature lymphoid cells. On the other hand, these fetal antigens may represent a lymphoid cell alloantigen system similar to if not the same as that described for human B-cells (26, 46). The PBL subpopulation does not appear to consist of activated lymphocytes. In 3 separate experiments each, isolated normal PBL were tested for fetal antigen expression 3 and 5 days after stimulation with the mitogens phytohemagglutinin and pokeweed. In all cases the percentage of cells fluorescing fell progressively below the control level as the cultures proliferated.

The chemical nature of these B-cell fetal antigens awaits elucidation. Preliminary experiments involving treatment of the live cells with trypsin or neuraminidase decreased antisera binding, suggesting that the fetal antigens may be glycoprotein in nature, rather than glycolipid as in some other systems (9). Appropriate absorptions with fetal calf sera and normal human sera eliminated the possibility that the antigens were nonspecific proteins adsorbed from the media. Despite the presence of Mycoplasma, the MOLT-4 line carried no fetal antigens, indicating that the antisera were not detecting these organisms. The involvement of known human fetal antigens remains to be explored fully. The fetal antisera show reactivity with both carcinoembryonic antigen and α-fetoprotein. However, analyses in sodium dodecyl sulfate-polyacrylamide gels of immune precipitates between antifetal sera and their respective radioiodinated fetal extracts indicate that 3 or 4 additional specificities are involved. It is possible that they detect fetal antigens characteristic of B-lymphocytes.

The fetal antigens could also reflect a viral product expressed at the B-cell surface. Most human B-lymphoblast lines are infected with the Epstein-Barr virus or possess its genome. Huebner et al. (14) have suggested that “virogene” products may be expressed in embryonic and fetal life, to be later reactivated in adult neoplasia. In this respect the detection of these fetal antigens in high concentrations on the surface of leukemic lymphocytes from patients with CLL is of great interest. Studies are in progress to determine the antigenic and molecular relationships between the fetal antigens expressed on cultured lymphoblasts and those on leukemic cells.

The biological significance of fetal antigens in general remains unknown, but their growing number and variability of expression during development attest to their importance. The expression of these fetal antigens on both cultured and neoplastic lymphocytes led us to examine their possible variation during the cell cycle. In Chart 1, B-lymphoblasts from a logarithmically growing culture were separated by slow-speed centrifugation at 4° on a linear 5 to 20% Ficoll density gradient (8), a procedure that fractionates the culture into cell cycle phases. The incorporation of tritiated thymidine (S phase). G cells lie above (to the left), and G2-M cells lie below (to the right).

Chart 1. Cell cycle-related variation in surface membrane expression of fetal antigens on cultured human B-lymphoblasts. Separation of logarithmically growing suspension culture on a linear 5 to 20% Ficoll density gradient. Arrow, peak of incorporation of tritiated thymidine (S phase). G, cells lie above (to the left), and G2-M cells lie below (to the right).

The demonstration of fetal antigens on the surfaces of subpopulations of lymphoid cells also raises the possibility that such substances might play a regulatory role in the immune response under certain circumstances. α-Fetoprotein, for example, has been shown to exert an immunosuppressive effect on antibody synthesis when administered in vivo (32). Moreover, in vitro it suppresses without cytotoxicity both the primary and secondary antibody response to sheep RBC (29). α-Fetoprotein has been shown as well to suppress certain T-cell-dependent functions in mice such as allogeneic and mitogen-induced lymphocyte transformation (30). A recent report describes binding of α-fetoprotein to murine T-cells but not B-cells (7). α2-H-globulin, a human fetal hepatic glycoferroprotein, has also been shown to be immunosuppressive (5). The material inhibited antigen- and mitogen-induced human lymphocyte transformation and blocked antibody synthesis in vivo by mice against sheep
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