Abstract. Normal morphogenesis and differentiation depend on the coordination of cell-cell and cell extracellular matrix (ECM) interactions. Integrins are a class of adhesion molecules that participate in the cell-cell and cell-substratum interactions and are present on essentially all human cells. All mammalian eggs express integrins at their surface, and the integrin α6β1 serves as a sperm receptor, mediating sperm-egg binding. In addition, certain integrin moieties appear to be regulated within the cycling endometrium; the expression of β1 integrins in the early proliferative phase is restricted to the glandular epithelium, whereas stromal cells in the midsecretory phase also express β1 integrins. The expression of β1 integrins increases at the time of implantation and remains high in decidua during early pregnancy. A disruption of the integrin expression is associated with certain types of infertility in women. The apical surface of the mural trophectoderm does indeed possess functional integrins, and trophoblast interactions with ECM proteins depend largely on the integrin family of adhesion receptors. Thus, integrins play particularly important roles in fertilization and embryogenesis, including the process of implantation. (Keio J Med 46 (1): 16-24, March 1997)

Key words: integrin, endometrium, decidua, embryo, implantation

Introduction

The attachment of cells to their surroundings is important in determining cell shape and in maintaining proper cell function and tissue integrity. Extracellular matrices are made up of an insoluble meshwork of protein and carbohydrate that is laid down by cells and that fills most of the intercellular spaces. Earlier studies have demonstrated that the trophectoderm cells of preimplantation mouse blastocysts have been shown to contain fibronectin as well as laminin. Furthermore, fibronectin and laminin, when individually precoated on tissue culture plates, promote in vitro attachment and outgrowth of mouse blastocysts in serum-free medium. Extracellular matrix (ECM) proteins produced by stromal or decidual cells are also important for endometrial structure and integrity and provide a site for trophoblast attachment. Loke et al demonstrated that human first trimester trophoblasts bound to laminin in vitro and, in addition, this protein can be seen to surround individual decidual cells in vitro and in vivo. These findings suggest that decidual laminin as well as fibronectin and collagen may provide the initial attachment sites for trophoblasts facilitating their penetration into the endometrium. However, the molecular basis of mammalian embryo implantation in the uterus is not well understood because of the complexity of the system and its inaccessibility to controlled experimentation at the biochemical level. Human decidua differentiation from the uterine stromal lining into active secretory tissue is induced by hormone stimulation during early pregnancy. The maternal decidua is in direct contact with the fetal trophoblast and therefore provides a hospitable environment for implantation of the blastocyst.

Isolation and characterization of cell surface receptors for ECM components has clarified the mechanism of the interactions of cells with the components of the ECM protein. These receptors are integral membrane glycoproteins, called integrins, that connect extracellular cell adhesion proteins to cytoskeletal components.
Integrins are heterodimers composed of different α subunits and a common β subunit and include cell surface receptors for fibronectin, collagen, and laminin. The β1 subfamily is known as VLA (very late antigen). The β1 integrin can pair with at least 9 different α subunits, forming ECM receptors with distinct specificities. Monoclonal antibodies directed to the different α and β subunits of integrin are useful for the initial characterization of the integrin profile of human cells. These reagents also facilitate assessment of the qualitative and quantitative alterations that occur in the expression of ECM proteins. The functions of individual integrins have been elucidated using cell adhesion assays and these monoclonal antibodies. The critical roles of integrins in differentiation, migration, and invasion of trophoblasts in mammals are emphasized. This review summarizes recent evidence concerning expression and modulation of integrins and signaling events mediated by integrins in fertilization, embryogenesis and implantation.

**Fertilization and Integrins**

The process of mammalian fertilization involves a cascade of cell-cell and cell-matrix interactions. Sperm and oocyte plasma membranes. Although differences have been reported as to the specific integrin subunits present on eggs from a particular species, there is complete agreement that the integrin α6β1 is present on the surface of oocytes from all mammalian species analyzed. A function-blocking anti-α6 monoclonal antibody abolishes sperm binding, but a nonfunction-blocking anti-α6 monoclonal antibody has no effect, suggesting a novel role for the integrin α6β1 as a cell-cell adhesion receptor that mediates sperm-oocyte binding. Furthermore, since integrins are well-known to transduce signals, binding of a sperm ligand to α6β1 on the oocyte could be a key event that initiates development of the embryo.

**Expression of Integrins in Endometrium and Decidua**

**Endometrial integrins**

Human endometrium is composed of distinct arrangements of cells of different lineages. These include endometrial glands, stromal cells, fibroblasts, lymphoid cells, endothelial cells, and smooth muscle cells which coat vessels of the endometrium. The complex structure of the endometrium undoubtedly requires an array of distinct molecules which contribute to cell distribution, cell trafficking and interaction of cells with each other and with the constituents of the endometrial meshwork consisting of collagen, fibronectin, laminin and other matrix proteins. Human endometrium undergoes a remarkable series of developmental changes during the menstrual cycle in preparation for embryonic implantation, changes that persist into early pregnancy. The phenomena of cyclic endometrial replenishment, implantation, gestation, and parturition may require specific cell-cell and cell-substratum interactions. The recent discovery that certain endometrial integrins exhibit cycle- and cell-specific patterns of expression has generated intense interest in this family of cell adhesion molecules and led to speculation that integrins may participate in the cascade of molecular events involved in the implantation process.

Several studies confirm the presence of β1 integrins on human endometrium and demonstrate that the expression is a dynamic process related to the menstrual cycle. The distribution of different α and β integrin subunits in human endometrial tissues at different stages of the menstrual cycle has been determined using immunohistochemistry, suggesting that some integrins normally undergo spatial and temporal changes with expression in the cycling endometrium, and that a disruption of this pattern may be associated with certain types of infertility in women.

The pattern of integrin expression in the endometrium during implantation is most interesting. Its principle
feature is apparent shift from epithelial to predominantly stromal expression. We recently demonstrated that the expression of β₁ integrins in the endometrium coincided with the ovarian changes, allowing a distinction between the early proliferative and midsecretory phases (Fig 1). The expression of β₁ integrins varied throughout the cycle, occurring predominantly during the secretory phase. The localization of β₁ integrins in the early proliferative phase was restricted to the glandular epithelium, whereas stromal cells in the midsecretory phase also expressed β₁ integrins. Recent studies have demonstrated that the expression of β₁ integrins in human endometrium increases at the time of implantation. Thus, certain β₁ integrin moieties appear to be regulated throughout the endometrial cycle; however, the mechanisms responsible for β₁ integrin regulation have yet to be established. We found that treatment of stromal cells in the proliferative phase with estradiol (E₂) and progesterone (P) increased the expression of β₁ integrins in vitro (Fig 1), and that the expression of β₁ integrins in midsecretory stromal cells was greater than that in early proliferative phase, suggesting that β₁ integrin expression in endometrium may be progesterin-dependent. The differential expression of β₁ integrins within different compartments of the endometrium reflects the different nature and function of these compartments.

Implantation occurs approximately 5–6 days after ovulation in humans as previously described by Hertig et al. Carefully synchronized embryonic and uterine receptivity is required for successful implantation; the interval during which these events first become coordinated may define the putative window of endometrial receptivity. One specific integrin, the α₅β₃ vitronectin receptor, appears on endometrial epithelial cells only after day 19 of the normal menstrual cycle; the onset of its expression corresponds to the opening of the putative "implantation window". A loss of normal α₅β₃ expression is associated with primary infertility and milder forms of the disease. These observations suggest that this integrin play a significant role in the implantation process. α₅β₃ is an unusual epithelial integrin and recognizes and binds to the RGD amino acid sequence found in vitronectin, fibronectin, von Willebrand's factor, and osteopontin. This integrin may participate in cell-cell interactions wherein both cells maintain the same cell surface integrin and bind a common bridging ligand. Trophoblast, like endometrium, also express α₅β₃ on its surface and osteopontin with two distinct RGD-dependent binding sites recognized by α₅β₃ is present in luteal phase endometrium. Thus, a mechanism of trophoblast-endometrial interaction that involves this integrin is plausible.

Decidual integrins

Human decidua differentiates from the uterine stromal lining into actively secretory tissue under hormonal stimulus of early pregnancy. The maternal decidua is in direct contact with the fetal trophoblast, and therefore provide a hospitable environment for implantation of the blastocyst. Wewer et al have demonstrated immunohistochemically and morphologically three separate subpopulations of decidual cells that may represent different stages of the human decidual cell lineage. Since decidualization appears to represent a continuum, ranging from stromal cells (<15 μm diameter) to hypertrophied mature decidual cells (>25 μm diameter), the expression of β₁ integrins on decidual cells may represent any or all of these stages of differentiation. The most prominent cell type in decidual tissues has been shown to be large, mature, epithelioid cells with a distinct pericellular basement membrane containing laminin, type IV collagen, fibronectin, and possibly other components. The pericellular distribution pattern of ECM around the individual decidual cells suggests that ECM receptors are present on the surface of decidual cells. Our previous studies using flow cytometric analysis reveals that decidual cells express high levels of the α₁ and α₂ subunits and moderate levels of the α₅ and α₆ subunits. In addition, the biosynthesis of β₁ integrins was demonstrated by metabolic labeling of cultured decidual cells and immunoprecipitation of the cell extracts with a specific antibody followed by SDS-PAGE (Fig 2). The expression of β₁ integrins in human endometrium increases at the time of implantation and remains high in decidua during early pregnancy. This indicates the presence of a certain degree of specificity, potentially mediated by β₁ integrins, which are the major family of ECM receptors on the surface of...
In vitro human decidual cells synthesize and secrete prolactin (PRL). Decidual PRL is identical to pituitary PRL on the basis of several criteria including immunologic properties, gel chromatographic elution pattern, bioactivity, and the ability of decidual PRL mRNA to hybridize pituitary PRL cDNA.\textsuperscript{42,43} Isolation of PRL-producing cells from human decidua has permitted identification of the cell type in the final preparation that is responsible for the PRL secretion.\textsuperscript{44} The enriched fraction of PRL-producing decidual cells isolated by Percoll gradients consists of a nearly homogeneous population of large, round mononucleated cells (>25 \( \mu \)m diameter) and exhibits greater expression of \( \beta_1 \) integrins on cell surfaces.\textsuperscript{35} These findings imply that the PRL-producing cells in human decidua during early pregnancy express cell surface \( \beta_1 \) integrins in specific decidual subpopulations. Mature decidual cells may be responsible for this expression of \( \beta_1 \) integrins, leading to the deposition of ECM proteins at the implantation site. Alternatively, increased expression of receptors in PRL-producing cells may lead to the morphologic differentiation of decidual cells.

Expression of Integrins in Embryos

ECM proteins play an important role during embryonic development, affecting cell growth, migration, and differentiation.\textsuperscript{3-5,45,46} The ECM component fibronectin is expressed after blastocoele formation in the rodent embryo and appears to be associated with migration of endodermal cells beneath the trophectoderm.\textsuperscript{45,46} Laminin \( \beta_1 \) and \( \beta_2 \) subunit, which are the earliest ECM constituents, are detected at the 2-to 4-cell stage.\textsuperscript{4,46-48} In human, \( \beta_1 \) integrin and laminin are also detected in embryos at the morula stage,\textsuperscript{49} while fibronectin and \( \alpha_5\beta_1 \) integrin are expressed on the surface of in \textit{vivo}-produced 8-cell bovine embryos in the presence or absence of soluble fibronectin.\textsuperscript{50} Thus, there is considerable diversity in the adhesion receptors and ECM ligands prior to blastocyst hatching. Since broadly reacting anti-integrin antibodies do not interfere with any aspect of preimplantation development,\textsuperscript{51} there is little evidence of ECM organization during this period. In fact, the first detectable adhesive events in the embryo, compaction, is independent of \( \beta_1 \) integrin in the mouse, whereas antibodies to the cell-cell adhesion molecule E-cadherin interfere with both compaction and primitive endoderm segregation.\textsuperscript{52}

It has been recently reported that mouse embryos produce a broad repertorie of ECM constituents and ECM receptors from the onset of development.\textsuperscript{27,53} Three basic integrins, \( \alpha_5\beta_1 \), \( \alpha_6\beta_1 \), and \( \alpha_5\beta_3 \), is expressed continuously by the embryo throughout early development, whereas five other \( \beta_1 \)-associated \( \alpha \) subunits, \( \alpha_1 \), \( \alpha_2 \), \( \alpha_3 \), \( \alpha_6A \) and \( \alpha_7 \), show developmentally regulated expression.\textsuperscript{27} Thus the embryo always has the potential to interact with fibronectin via \( \alpha_5\beta_1 \) and \( \alpha_5\beta_3 \) integrins, laminin via \( \alpha_6b\beta_1 \) and \( \alpha_5\beta_3 \) integrins and vitronectin via \( \alpha_5\beta_3 \) integrin. The major point of regulation of integrin expression is the late blastocyst stage. Expression of \( \alpha_2 \), \( \alpha_6A \), and \( \alpha_7 \) mRNA begins at the late blastocyst stage before implantation, whereas \( \alpha_1 \) expression begins with embryo outgrowth or implantation. At least three subunits, \( \alpha_1 \), \( \alpha_6A \) and \( \alpha_7 \), are specific to extraembryonic tissues, reflecting that trophoblast and endoderm cells have the most extensive interactions with ECM at the expanded blastocyst stage, and may therefore require the greatest diversity of receptors. The variety of matrix receptors\textsuperscript{27,53} and ligands\textsuperscript{3-5,45-50} expressed in the pre-implantation periods are likely to be important for basement membrane formation on the inner surface of the trophectoderm and between the primitive ectoderm and primitive endoderm of the late blastocyst.\textsuperscript{27} However, there is little evidence that integrin-mediated interactions are involved in other aspects of preimplantation development.
Mechanism of Integrin-mediated Regulation in Implantation

Trophoblast integrins

Implantation of the embryo is mediated by a specialized population of the cells, trophoblast, which arise from the trophectoderm, the outer layer of epithelial cells that encloses the blastocoel cavity and the inner cell mass of the preimplantation blastocyst. Conversion of the epithelial trophectoderm to invasive trophoblast begins at the late blastocyst stage, and comprises both a change in adhesive behavior and the onset of motility. The invading trophoblast would encounter a variety of ECM ligands during implantation. The invasiveness of trophoblast cells has been modeled in vitro by culturing mouse blastocysts on surfaces treated with ECM proteins known to be present in the endometrium, including fibronectin. Mouse primary trophoblast cells appear to interact with fibronectin exclusively through the RGD recognition site, indicating that the fibronectin receptor is expressed on the surface of trophoblast cells. In addition to fibronectin, trophoblast outgrowth is also mediated by the RGD sequence in vitronectin, collagen, and entactin. Delineating the biological mechanism and developmental regulation of trophoblast adhesion in vitro is an important step toward understanding the very complex process of implantation.

The ability to attach to the substrata of ECM proteins is acquired during trophoblast differentiation; early blastocysts cultured on substrata of ECM do not adhere and spread, whereas late blastocysts form an embryo outgrowth, consisting of monolayer of spreading trophoblasts with the inner cell mass. Trophoblast interactions with ECM proteins depend largely on the integrin family of adhesion receptors, as broad spectrum anti-integrin antibodies block trophoblast attachment and outgrowth on fibronectin, laminin, or collagen IV-coated substrata. The changes in trophoblast adhesive and migratory behavior that occur at the time of implantation may therefore stem from changes in the expression or distribution of integrin receptors.

The apical surface of the mural trophectoderm does indeed possess functional integrins and have provided a novel experimental model for exploring the initial interactions between an implanting blastocyst and adhesive components of the ECM. At least three integrin α subunits, α1, α6A, and α7, are newly expressed when the blastocyst becomes attachment competent. The α1 integrin subunit becomes detectable only after trophoblast outgrowth, suggesting that its expression is a response to contact with ECM. The α1, α6A (an alternatively spliced form of the α6 subunit), and α7 subunits are detected in the extraembryonic ectoplacental cone and differentiating secondary trophoblast. Thus, differentiation of trophoblasts is accompanied by the onset of expression in these cells of three additional integrins, providing an expanded ability for trophoblasts to interact with ECM proteins.

Mouse blastocyst outgrowth on ECM proteins is mediated by trophoblast expression of several integrin receptors, possibly in concert with one another. Trophoblast cell adhesion and migration mediated by fibronectin appear to involve primarily the interaction of cellular receptors with the RGD recognition site in the central cell-binding domain. Comparable outgrowth is observed on substrates consisting of intact fibronectin, a fragment of fibronectin containing the central cell-binding domain, or a recombinant protein constructed with multiple copies of the decapetide encompassing the RGD cell recognition site. The mechanism of this interaction with fibronectin clearly involves the RGD recognition sites, and may not require other regions of the fibronectin polypeptide. In trophoblast cells adhering on fibronectin, Yeilian have identified subunits of several RGD-dependent integrins that recognize fibronectin, including the α3, α5, αv, α1, β1, and β3 subunits. Blastocyst outgrowth on fibronectin is partially inhibited by antibodies against the β1, β3, and α5 subunit, suggesting that integrins of the β1 and β3 classes play a functional role in trophoblast adhesion to fibronectin. In the recent study, furthermore, function-blocking antibodies specific for the α5, αv, β1 or β3 integrin subunit have been shown to inhibit the fibronectin binding activity of intact blastocysts, indicating that initial recognition of fibronectin by primary trophoblast cells requires apically located integrins composed of the α5β1 and αvβ3 heterodimers. Because mouse primary trophoblast cells are capable of adhering to substrates through interaction with other adhesion-promoting peptide sequences, the array of ECM receptors expressed by the invasive trophoblast cell may be dependent upon the molecules that are present in the substrates. Thus, trophoblast cells may constitutively express a variety of receptors that permit recognition of many ECM components. During implantation, the ability to adhere to many ECM components may be advantageous since the composition of the ECM that the trophoblast cells engage changes as they penetrate the basement membrane, invade the stroma, and infiltrate blood vessels.

The increased number of receptors could result from increased receptor synthesis or from the movement of sequestered receptors to the apical cell surface. Reports from other cell systems have documented increased ligand affinity due to conformational changes in integrins that were either dependent on or independent of a signal transduction event. Ligand-mediated potentiation of blastocyst adhesion does not appear to directly result from a conformationally induced change in receptor affinity but is dependent on metabolic energy, cytoskeletal integrity, and protein trafficking. The low number of
receptors initially present on the blastocyst surface is perhaps inadequate for adhesion but may be able to transduce intracellular signals that initiate the mobilization of additional receptors. Protein translocation to the apical plasma membrane would require both energy and an intact cytoskeleton. Schultz and Armand\(^59\) have further provided evidence for the role of protein trafficking in regulating fibronectin binding activity with the reversible inhibition of ligand-mediated potentiation by brefeldin A, an inhibitor of protein trafficking. Posttranslational processing of integrins may require several hours,\(^53\) making it impossible for cells to quickly become adhesive through de novo receptor synthesis. It has been suggested that differential processing of integrin oligosaccharides may regulate their export to the plasma membrane and control fibronectin binding activity.\(^53\) Receptor storage and trafficking offers a means of rapidly modulating cell adhesiveness that would certainly benefit invasive trophoblast cells during their migration through the endometrial ECM.

Key mechanisms underlying various steps in trophoblast invasion into basement membrane and stroma are analogous to those involved in tumor cell invasion.\(^64\) In the invasion of host tissue by cancer cells, a stepwise progression has been postulated; the first stage is achieved by the specific attachment of cancer cells to ECM proteins and basement membrane components such as laminin via tumor cell surface receptors.\(^65\)\(^,\)\(^66\) Integrin-related receptors for laminin and type IV collagen also have been implicated in the attachment process.\(^67\) These data suggest that $\beta_1$ integrins on embryos, which interact with ECM components produced by decidual cells, may be involved in the process of early attachment of blastocysts during implantation.

**Decidual integrins**

The mechanism by which $\beta_1$ integrins promote trophoblast outgrowth may be related to their known adhesive role and their participation in cell attachment/detachment and migration of cells.\(^2\)\(^,\)\(^11\)\(^,\)\(^12\) ECM proteins are expressed during early embryogenesis: Laminin B1 and B2 chains appear at the four-cell stage,\(^4\)\(^,\)\(^5\)\(^,\)\(^45\) and fibronectin and type IV collagen are first detected at the blastocyst stage.\(^3\)\(^,\)\(^4\) In addition, isolated trophoblasts in primary culture have been demonstrated to synthesize and secrete fibronectin molecules bearing a unique glycopeptide domain within the type III connecting segment.\(^68\) This has been classified as the oncofetal fibronectin class and may mediate implantation and placental-uterine attachment throughout gestation.\(^68\) $\beta_1$ integrins on human decidual cells may be important in mediating the organization of ECM proteins derived from embryos during the early stage of implantation, thereby connecting

![Fig 3](image-url)
the ECM framework to the intracellular cytoskeletal structures.²¹,¹² It is also possible that expression of β₁ integrins on decidual cells may prepare the uterine wall for blastocyst invasion. Mouse blastocysts are capable of attaching to and forming extensive trophoblast outgrowth on human decidual cells in vitro (Fig 3).⁶⁹ Because blastocysts grown in vitro on cultured human decidual cells display attachment and outgrowth of trophoblasts in the presence of a mouse monoclonal IgG₁ antibody, we chose this system to evaluate the factors that regulate trophoblast differentiation. Attachment of the blastocysts to the cultured decidual cells appears to be a prerequisite for further outgrowth of trophoblasts. Outgrowth, but not attachment, of embryos on decidual cells was inhibited in a dose-dependent manner by the addition of an antibody recognizing the β₁ chain (Fig 3), suggesting that β₁ integrins are important in blastocyst development and differentiation following attachment.⁶⁹

Monoclonal antibodies against the β₁, α₁, α₂, α₅, and α₆ subunits affected embryo outgrowth, but not attachment, suggesting that blastocyst attachment and outgrowth may be mediated by different mechanisms. Subsequent spreading of trophoblasts involves a number of cellular events that are necessary to produce morphologic changes and migration of the cells.⁷⁰ Farach et al⁷¹ also have reported that soluble heparin inhibits mouse embryo attachment and outgrowth on fibronectin and laminin, and that substrates of a heparin-binding protein, platelet factor 4, support attachment, but limited outgrowth. Purified cell-substratum adhesion glycoprotein, GP140, which participates in the attachment of somatic cells to the substratum, also has been demonstrated to mediate trophoblast attachment of mouse blastocysts.⁵² In recent reports, increased epithelial vitronectin receptor, αβ₃ in normal menstrual cycles has been shown to correlate a putative "implantation window" postulated to exist within the secretory phase.³²,³⁷ Since both trophoblast and endometrium express αβ₃ on their surface,³⁹,⁴⁰ this epithelial integrin may be involved in the endometrial-trophoblast interaction that takes place during early embryonic attachment. These studies imply that outgrowth is mediated primarily by mechanisms that involve the expression of β₁ integrins on decidual cells; however, attachment may be mediated through heparin or heparin-sulfate-containing moieties or other cell surface adhesion molecules on endometrial epithelial cells.

β₁ integrins also may maintain the in vitro monolayer continuity of human decidual cells. When confluent decidual cells are incubated with increasing concentrations of a monoclonal antibody recognizing the β₁ chain, discontinuity of the decidual cell monolayers progressively increases.⁶⁹ Eventually, substantial holes appear, and the monolayer subsequently become detached. These data are consistent with the results of a recent study in which the αβ₃ and αβ₁ integrins are localized to cell-cell borders in confluent human umbilical vein endothelial cell monolayers; their corresponding antibodies alter the integrity of the endothelial cell monolayer and affect the permeability barrier.⁷² Monolayer integrity requires the establishment and maintenance of both cell-cell and cell-matrix contacts during in vitro culture.⁷³ It is possible that some members of the β₁ integrin family on decidual cells interact with other intercellular molecules to form lateral junctions to maintain the monolayer integrity. We recently demonstrated the presence of β₁ integrins in freshly isolated human decidua using immunohistochemistry.⁵³ The β₁, α₁, α₂, α₃, and α₅ subunits of the integrins are localized on the outer boundaries of decidual cells corresponding to sites of intercellular contact. The presence of β₁ integrins on human decidua is consistent with the finding that this class of integrin is expressed in the human endometrium in a dynamic process relating to the menstrual cycle.³¹-³³,³⁵,³⁷ These data suggest that β₁ integrins may participate in the maintenance of decidual cell continuity in vivo as well as in vitro.

A recent study has demonstrated that insulin-like growth factor binding protein-1 (IGFBP-1) binds specially by its Arg-Gly-Asp(RGD) sequence to the α5β₁ integrin receptor.⁷⁴ Irwin et al⁷⁵ also have reported that decidualized stromal cells secrete high levels of IGFBP-1, and placental cytotrophoblasts attach to the surface of cultured stromal cells. These findings suggest that maternal IGFBP-1 may affect the interaction of placental trophoblast with ECM proteins in the endometrial stroma, and thereby modulate its invasion into the maternal decidua.⁷⁵ Further investigations of the interactions of IGFBP-1 with integrins in the process of implantation will be an important component of future work.

References

8. Wewer UM, Faber M, Liotta LA, Albrechtsen R: Immunohistochemical and ultrastructural assessment of the nature of the


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