

Mini review

## ONCOFETAL ANTIGEN/IMMATURE LAMININ RECEPTOR PROTEIN IN PREGNANCY AND CANCER <sup>¶</sup>

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In Memory of Professors Joseph H. Coggin and James W. Rohrer

**Abstract:** The 37-kDa immature laminin receptor protein (iLRP) is a species-conserved, universal immunogenic protein that is expressed in all thus-far examined embryonic and early fetal cells of inbred and outbred rodents. It has also been identified in human concepti. It is altered through normal maturation processes to become a non-immunogenic 67-kDa dimeric mature laminin receptor protein (mLRP) in mid- to late gestation in the mammalian fetus. This antigen ceases to be expressed as an active autoimmunogen in the full-term fetus and in the normal differentiating tissues and organs of the neonate or adult organism, apparently due to dimerization, but it is re-expressed as an immunogenic monomer in tumor cells. In this review, we highlight the known mechanisms of immune responses with particular emphasis on the possible role of the 37-kDa oncofetal antigen/immature laminin receptor (OFA/iLRP) in both pregnancy and cancer.

**Keywords:** Cancer, Galectins, Immature laminin receptor, Oncofetal antigen, Pregnancy

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<sup>¶</sup> Invited paper

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Abbreviations used: APC – antigen processing cell; CTL – cytotoxic T lymphocyte; DC – dendritic cell; DMBA – 2,4-dimethoxybenzaldehyde; FasL – Fas ligand; Gal – galectin; IFN – interferon; IL – interleukin; iLRP – immature laminin receptor protein; MHC – major histocompatibility complex; mLRP – mature laminin receptor protein; NK – natural killer; OFA – oncofetal antigen; Tc – T cytotoxic; TCR – T-cell receptor; TGF – transforming growth factor; Th – T helper; TNF – tumor necrosis factor; Treg – regulatory T cells; Ts – T suppressor; TSTA – tumor-specific transplantation antigen

## INTRODUCTION

Although the fetus represents a foreign entity to the maternal immune system, this “natural” allograft is not normally rejected. Sixty years ago, Medawar [1] first proposed that a state of immunological tolerance should occur during pregnancy to protect the semi-allogeneic fetus from immune attack by the mother. Medawar’s conclusion — that the single most important factor ensuring the success of gestation is the elaboration of an immunological barrier by the placenta between the fetus and its mother — remains substantially valid to this day. However, this barrier is an active one and not passive or neutral as originally presumed. This active mechanism prevents fetal tissues from being recognized as foreign and/or from being rejected by the cells of the maternal immune system [2]. In early pregnancy, decidual maternal lymphocytes are activated and they recognize the semi-allogeneic fetus. Immune regulatory systems work to prevent fetal rejection. Recent data showed that parts of the immunoregulatory system, such as CD4+CD25+ regulatory T (Treg) cells, Th3 cells, Tr1 cells, regulatory NK cells, and CD8 suppressor cells, play very important roles in inhibiting maternal T cell or NK cell fetal attack, and are thus crucial to maintaining a successful pregnancy [3, 4]. The following is a brief description of the main systems involved in pregnancy, and those involved in cancer.

### **Th1/Th2 balance**

T helper (Th) cells are central to the development of an immune response. They activate antigen-specific effector cells and recruit cells of the innate immune system, such as macrophages and mast cells. Two main Th cell subtypes exist, Th1 and Th2.

Th1 cells, characterized by secretion of IFN- $\gamma$  and TNF- $\alpha$ , are primarily responsible for activating and regulating the development and persistence of CTL. A Th2-type reaction at the maternal–fetal interface, generating non-inflammatory cytokines (IL-4 and IL-10) is compatible with normal pregnancy. However, a Th1-type reaction in the placenta, mainly generating inflammatory responses (IL-2 and IFN- $\gamma$ ), is often correlated with miscarriages [5].

Implantation of the blastocyst in the maternal endometrium occurs in a Th1-dominant cytokine milieu, but the placental trophoblast is capable of inducing a shift of the Th1/Th2 balance toward Th2 as a mechanism in achieving maternal tolerance to the fetus [6, 7]. In cancer, Th1 cells activate antigen-presenting cells (APC) and induce limited production of the type of antibodies that can enhance the uptake of tumor cells into APC. Th2 cells favor a predominantly humoral response. Particularly important during Th differentiation is the cytokine environment at the site of antigen deposition or in the local lymph node. Th1 commitment relies on the local production of IL-12, and Th2 development is promoted by IL-4 in the absence of IL-12 [8].

**Dendritic cells**

Dendritic cells (DCs) serve as antigen-presenting cells with the unique ability to induce primary immune responses. Just as lymphocytes comprise different subsets, DC subsets have been identified that differentially control lymphocyte function. DCs may also act to induce immunologic tolerance and regulation of T cell-mediated immunity. Antigen-driven proliferation of Treg cells is evident in the lymph nodes draining the uterus, and might also occur within the decidual tissue, which has abundant populations of mature myeloid DCs capable of presenting trophoblast cell antigens. These DCs express markers indicative of a tolerogenic phenotype [9]. Tumor-associated macrophages and DCs could also play an important role in inhibiting immune responses and chronic inflammation [10], which has been linked to the development and progression of cancer [11]. Both tumor-associated macrophages and DCs promote tumor growth either by secreting immune suppressive cytokines, including interleukin-10 (IL-10), transforming growth factor- $\beta$  (TGF- $\beta$ ) and IL-1 $\beta$ , or by inducing Treg cell differentiation [12].

**Regulatory T cells**

The dialogue between Treg cells and tolerogenic DCs is pivotal in the activation and expansion of Treg cells [13]. Like all T cells, Treg cells require ligation of their TCR with cognate antigen and IL-2 in order to differentiate from naive CD4<sup>+</sup> T-cell precursors. Treg cell suppression is antigen-specific, and Treg cells can be maintained and expanded *in vivo* in the presence of their cognate antigen for the TCR [14]. Treg cells increase in number in the lymph nodes draining the uterus from as early as 2 days after mating whereas elevated blood levels do not become evident until after implantation [15]. Interestingly, the increase in Treg cells is not sustained throughout pregnancy but progressively declines from mid-gestation to return to non-pregnant levels by fetal delivery at term [16]. CD8<sup>+</sup> regulatory cells have also been implicated in the suppression of fetal immune rejection from early pregnancy in mice [17]. Regulatory T cells have a detrimental role in cancer immunotherapy because they accumulate in the tumor microenvironment and suppress immune responses [18–20].

**Galactins**

Galectins, a family of structurally related proteins, have been implicated in immune maturation and modulation through various mechanisms [21]. Galectin-1 has demonstrated selective anti-inflammatory and immunoregulatory effects by controlling immune cell trafficking, “fine-tuning” dendritic cell physiology, or regulating T-cell fate. These regulatory functions may contribute to fulfilling the needs for immune cell homeostasis, including the preservation of fetomaternal tolerance [22]. Galectin-1-deficient mice showed higher rates of fetal loss compared to wild-type mice in allogeneic matings. Treatment with recombinant galectin-1 prevented fetal loss and restored tolerance through multiple mechanisms, including the induction of tolerogenic dendritic cells,

which in turn promoted the expansion of IL-10-secreting regulatory T cells in vivo. Galectin-3, a component of the mature laminin receptor protein (mLRP) may function as an immune regulator to inhibit T-cell immune responses and promote tumor growth, thus providing a new mechanism for immune tolerance [23].

#### **Oncofetal antigen is immature laminin receptor**

Clones coding for OFA have been isolated from a cDNA library of MCA-1315 murine fibrosarcoma and sequenced [24]. The predicted amino acid sequence of the protein (295 amino acids) is essentially identical (99.9%) to precursor or immature laminin receptor protein (iLRP) [24, 25]. The mature form (mLRP) is a 67-kDa dimeric acylated protein that associates with galectin-3 [26–28]. mLRP, expressed in normal adult cells, is not immunogenic in the host, but iLRP, which is expressed in cancers and in the early embryo/fetus of rodents and humans, arouses T-cell and B-cell responses in autologous hosts during pregnancy and oncogenesis [20, 29–33]. Mature LRP is widely expressed in certain normal adult cells, which must associate with laminin in basement membranes in their specialized function [26–28]. 37-kDa iLRP from rodent and human tumors is conserved with only a 2-amino acid difference in the sequence between them [24, 25]. Precursor T cells with the potential to recognize mLRP as a non-self protein are apparently deleted at thymic maturation to render the adult host incapable of responding to autologous mLRP to limit autoimmune reactions [24]. Precursor iLRP-specific T-lymphocytes are apparently not deleted at thymic maturation, so the adult host manifesting re-expression of the iLRP in emerging tumor cells can respond producing CD4 Th1, CD8 Tc and Ts lymphocyte OFA/iLRP-specific clones in vivo [24]. Both recombinant iLRP and the purified native protein from murine tumors or fetuses restimulate OFA-specific T-cell subclasses (Tc, Th1, and Ts) from irradiated RFM mice [30], MCA-mouse sarcoma bearers [24], and human cancer patients [31].

#### **Autoimmunogenicity of 37-kDa OFA/iLRP to pregnant mothers**

The expression of iLRP in the rodent and human fetus is phase specific. It is expressed through early to mid-gestation (mouse: day 13; hamster: day 11; human: end of 2<sup>nd</sup> trimester). Beyond these time points, iLRP ceases to be expressed as a detectable immunogen to elicit T-cell immunity or to react with anti-iLRP mAbs [29, 34]. Full-term fetal cells of mice (> 13 days) and hamsters (> 11 days) are not killed by iLRP-specific T-cells, whereas early fetal and embryo cells are killed [35].

The expression of 37-kDa iLRP is restricted to some embryo/fetal cells. Its expression on fetal cells of mice at day 9 of gestation is 20% and decreases to 5% at day 13 [36]. It is not detectable by day 14 of development in rodents. It is plausible that iLRP is converted to non-immunogenic mLRP and not processed as a T-cell immunogen in the blastocysts when they begin to form the three germ layers [29]. iLRP-expressing embryo cells in mammals may participate in invasive trophoblast formation at the uterine wall [37]. This view is supported by

the recent finding that anti-iLRP antibody blocked mouse embryo implantation by preventing embryo trophoblast cell invasion and migration through the uterine decidual basement membrane-like extracellular matrix, which has a high laminin content [38]. Predetermined embryo cells of mammals are reported to move and relocate within the developing embryo in a genetically programmed, development-directed, invasive fashion to make the normal anatomical structures in the emerging fetus.

The expressions of iLRP on the rodent fetus or when re-expressed in tumors serve to induce cross-reactive antibody and cross-protective T cell-mediated immune responses in syngeneic hosts irrespective of the source of iLRP. Pregnant syngeneic inbred mice and hamsters express antibodies to iLRP, which cross-reacts with iLRP re-expressed on a variety of sarcomas, leukemias and carcinomas. These pregnant mice or hamsters also carry cytotoxic T cells that can confer adoptive resistance to normal syngeneic rodents challenged with iLRP+ tumor cells induced by viral and chemical carcinogens [24, 25, 35, 39].

Other investigators [40] have subsequently reported that pregnancy in inbred rats yielded maternal lymphocytes that mediated protection against iLRP+ DMBA-induced, primary mammary cancer. Splenocytes from pregnant rats but not from non-pregnant, nulliparous females were cross-protective and cytotoxic to several mammary tumors tested. Modest to low protective activity was detected among maternal splenocytes for more than 36 days postpartum in primiparous female rats. However, when the splenocytes were re-stimulated with irradiated tumor cells *in vitro*, the protective Tc cells were significantly reactivated against the shared antigen on rat carcinomas [40].

Additionally, it was recently reported that a high percentage of pregnant women, but not nulliparous women, showed evidence of cross-protective sensitization to an unknown antigen present on breast, ovarian and endometrial carcinomas. This study further suggests that maternal sensitization to embryo-associated immunogen(s), including fertilized ova, which express iLRP *in utero*, may be responsible for immunologically driven abortion in some pregnant rodents [41].

The expression of iLRP in early embryo cells elicits maternal anti-iLRP antibodies and cytotoxic T cells, which have the capability to protect the mother from iLRP+ embryo or fetal cells, which are known to escape into maternal circulation via the placenta. Later in pregnancy, another subclass of iLRP-specific CD8+ T-lymphocytes appears in the maternal blood, spleen and possibly other lymphatics draining the uterus. These cells lack cytotoxicity and secrete the cytokine IL-10. The IL-10 released by these T suppressor (Ts) lymphocyte clones could impair the anti-fetal cytotoxicity of Tc lymphocytes, secreting interferon- $\gamma$  (IFN- $\gamma$ ) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), which are specific for iLRP and possibly all Tc lymphocytes capable of killing fetal cells, including those directed specifically against paternal MHC antigens (Fig. 1).

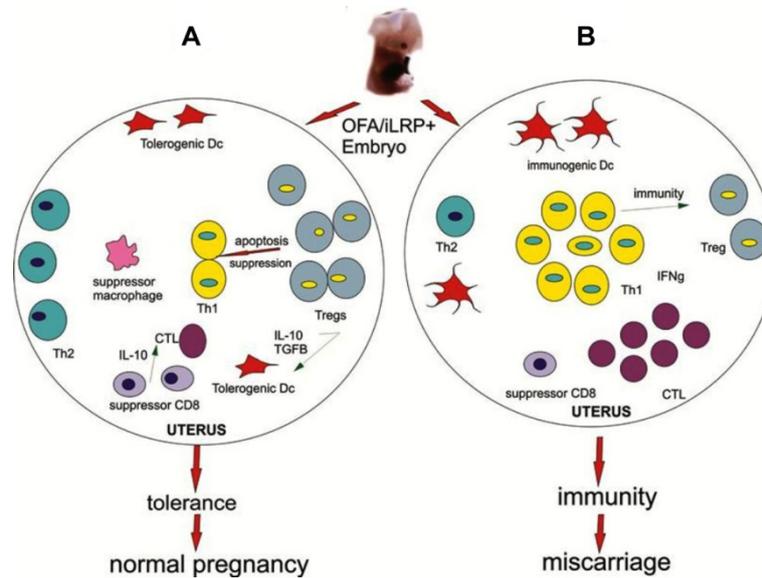


Fig. 1. A simplified view of the immunologic processes taking place in the uterus of a successful pregnancy and those leading to a miscarriage. Panel A – OFA/iLRP antigen released from trophoblast cells through shedding of debris may be taken up and displayed by maternal tolerogenic dendritic cells (DCs) within the uterus. After encountering their cognate antigen and in the presence of key cytokines (IL-4 and IL-10), naïve CD4 Th0 cells differentiate and develop mainly into Treg cells. An adequate number and function of Treg cells act to suppress Th1-mediated maternal attack of the semiallogeneic conceptus. Treg cells probably secrete IL-10 and TGF- $\beta$  and induce T-cell (Th1 and CD8+) tolerance through apoptosis or anergy. Suppressor CD8+ cells secrete IL-10, which suppresses CTL. Panel B – OFA/iLRP antigen may be taken up by immunogenic DCs within the uterus. After encountering their cognate antigen and in the presence of the proinflammatory cytokines IL12, CD4+ Th0 cells differentiate into Th1 cells. A placental Th1-type reaction, which mainly generates inflammatory responses (IL-2 and IFN- $\gamma$ ), correlates with miscarriages. Deficiency in Treg cell numbers and/or suppressive function is associated with miscarriage.

### Autoimmunogenicity of 37-kDa OFA/iLRP in syngeneic rodent and human tumors

iLRP is re-expressed in the tumors of rodents and humans during early transformation induced by oncogenic viruses, X-ray and UV exposure and chemical carcinogenesis [35], and in so-called spontaneous mouse lymphomas in old, normal mice [42]. iLRP is important to the tumor cells for invasion and metastasis [26], and most metastatic human tumors express increased amounts of this protein [43]. While early studies were confined to rodent tumor and pregnancy models, recent work has been focused on human malignancies, such as head and neck cancer [44], breast cancer [31], renal cancer [32, 45], hematological malignancies [33, 46–48], and several other types of cancer [34].

During tumor development, not only iLRP-specific, MHC-restricted effector T cells (CTL and Th1), but also CD8 suppressor T cells (IL-10-secreting) are induced [19, 31]. The secreted IL-10 inhibits CTL cytotoxic activity and IFN- $\gamma$  secretion by both CTL and Th1 cells (Fig. 2) [19]. Rodent tumor bearers and human breast cancer patients produce a vigorous CTL and Th1 response to iLRP during tumor development [20, 31]. iLRP begins to be expressed in tumor cells early in their transformation [42]. Anti-iLRP CD4 and CD8 lymphocytes were generated from peripheral blood T lymphocytes of breast carcinoma patients.

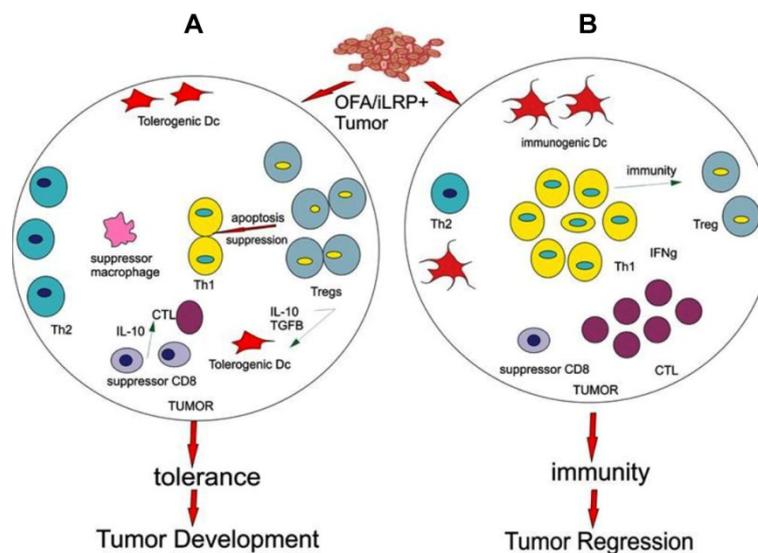


Fig. 2. A simplified view of the immunologic processes taking place in the tumor microenvironment and leading to tumor development or tumor regression. Panel A – Immature DCs in the tumor microenvironment are not conducive to the activation of antitumor immune responses due to the milieu of tumor-derived local immunosuppressive cytokines, such as TGF- $\beta$  and IL-10, which induce dampening of T cells and the augmentation of regulatory T (Treg) cell function. Reduction in the proliferation of T cells (Th1, Th2 and CTL) by suppression or apoptosis, and stimulation of Treg cell proliferation impede immune surveillance and ultimately induce anergy and favor tumor development. Panel B – Conversely, Dcs infiltrating the tumor microenvironment and monitoring the presence of tumor antigens (i.e., OFA/iLRP) may be activated. Activated DCs present the captured antigen to T cells in the secondary lymphoid organs, thus initiating and amplifying the immune response and triggering a maturation program that includes expression of multiple costimulatory molecules and proinflammatory cytokines (IFN- $\gamma$ , TNF- $\beta$ ) that result in efficient priming of effector T-cell responses. IFN- $\gamma$  increases MHC-I expression and antagonizes the immunosuppressant activity of TGF- $\beta$ . Tumor-specific CD4+ T cells and their subtypes (Th1, Th2), as well as cytotoxic CD8+ T cells, are directly involved in mediating in vivo antitumor immunity and tumor regression.

All of the CD4, iLRP-specific T-cell clones were Th1 cells which secreted IFN- $\gamma$ , but not IL-4 or IL-10 upon stimulation with irradiated, autologous breast carcinoma cells in the presence of irradiated, autologous antigen-presenting cells plus IL-2. The CD8+, iLRP-specific T-cell clones established from the breast cancer patient peripheral blood were split in their cytokine profiles. Some of the CD8 clones secreted IFN- $\gamma$  but not IL-4 or IL-10 upon stimulation with irradiated, autologous breast carcinoma cells. These clones were also cytotoxic to autologous breast carcinoma cells. The CD8, iLRP-specific suppressor T-cell clones that were not able to kill autologous breast carcinoma cells in a typical cytotoxicity assay did not secrete either IFN- $\gamma$  or IL-4, but they did secrete IL-10. However, immunization with iLRP in a mode that only or at least primarily induces Th1 and cytotoxic CD8 T cells could be used in cancer immunotherapy. One such mode would be by immunizing with autologous dendritic cells pulsed with iLRP or iLRP peptides that induce Th1 and cytotoxic T cells, but not with IL-10-secreting CD8 T cells [47, 49]. The *in vivo* antitumor efficacy of iLRP was also demonstrated by immunization of BALB/c mice with recombinant iLRP entrapped in liposomes and challenge with a tumorigenic dose of murine fibrosarcoma MCA1315 cells [50].

Immunization of BALB/c mice with syngeneic, bone marrow-derived mature dendritic cells (DC) which were pulsed with either intact iLRP or mixtures of two CTL clone-activating iLRP peptides inhibited MCA1315 fibrosarcoma cell lung metastasis and growth. However, immunization with two Ts clone-activating iLRP peptides reduced the inhibition of metastatic growth significantly [49]. This shows the ability for direct immunization with DCs pulsed with intact iLRP or iLRP CTL clone-activating peptides to limit tumor growth and metastasis *in vivo*. They also demonstrate differences in cytokine production and thus, effector function, induced by different iLRP peptides presented *in vivo* by DCs [49]. Immunization with DCs pulsed with OFA/iLRP+ renal cell carcinoma lysate prolonged the life of terminal renal cell carcinoma patients 4- to 6-fold longer than their typical lifespan with metastatic renal cell carcinoma [32]. Also, the disease process in those patients is either stable or cured. This therapeutic effect was apparently due to iLRP immunity induced by the DCs, as suggested by the finding that those patients with a Th1 response to iLRP were the only ones in which remission or stabilization of the disease occurred [32].

iLRP-specific cytotoxic T lymphocytes, generated from healthy HLA-A\*0201-positive volunteers, were capable of killing iLRP-expressing hematologic targets, including several lymphoma and leukemia cell lines, as well as fresh leukemic targets from patients with acute myeloid leukemia (AML) and chronic lymphatic leukemia (CLL), indicating that iLRP-derived peptides are naturally processed and presented by hematologic tumors [46]. Two distinct HLA-A\*0201-specific iLRP peptide-epitopes were identified and characterized, using Ag-specific CTLs that were generated by *in vitro* priming with peptide-pulsed monocyte-derived DCs [47]. They also demonstrated that iLRP peptide-specific CTLs obtained from healthy donors and patients with AML and

CLL elicited Ag-specific HLA-A\*0201-restricted cytolytic activity against several hematological tumor cell lines and freshly isolated AML and CLL tumor cells. Furthermore, by detecting iLRP-specific T lymphocytes in patients with CLL and multiple myeloma (MM) in an early stage of disease but not in patients with progressive disease, iLR-specific CTLs can play a role in controlling iLRP-expressing tumor cells [47].

The presence of iLRP-specific antibodies in the sera of untreated patients with CLL, and in patients after allogeneic transplantation of blood stem cells was shown by Friedrichs et al. [33]. They also showed that progression-free survival in CLL patients is associated with the presence of iLRP-specific humoral immune responses. The presence of both IgG and IgM isotypes suggests the involvement of a class switch promoting CD4 Th cells as evidence of a coordinated immune response against iLRP. The functionality of these antibodies and the recognition of extracellular epitopes of the iLRP sequence have significant implications for the development of immunotherapeutic approaches targeting iLRP+ tumor cells [33].

## CONCLUSION

Immature rather than mature LRP appears to play a significant role in regulating host tumor resistance by stimulating anti-iLRP-specific cytotoxic Tc lymphocyte subclasses and anti-iLRP specific Ts and Th1 T-cell responses during tumor development in vivo [19, 20, 30]. iLRP in high doses stimulates CD8 suppressor T-cell (Ts) lymphocytes which secrete IL-10 [19]. These Ts lymphocytes have the capacity to suppress cytolytic CD8 T cells mediating anti-iLRP-specific effector function, as well as TSTA-specific Tc cells by secreting IL-10 in the tumor microenvironment [19]. This appears to be a significant mechanism by which tumor cells evade host Tc-mediated tumor resistance [19, 20, 30].

iLRP expression during fetal development enables fetal cells to relocate in the trophoblast and emerging placental cells, invading the uterine wall. This creates a serious potential problem for the maternal host as such invasively endowed fetal cells are capable of producing tumors in the mother if not eliminated by her T-cell immune response. This hypothesis can only be validated if the maternal anti-iLRP-specific T-lymphocyte interactions are directed to the normal embryo and the fetal cell expression of iLRP during fetal development is controlled by regulatory mechanisms, provided by iLRP specific CD8-T suppressor cells [19], which protect the fetus from these cytotoxic T cells until the immunogenic iLRP is altered to its non-immunogenic form through maturation to mLRP in term fetal cells. Additionally, it is advisable to study the qualities and distribution of the maternal T cell-mediated protective responses occurring in the pregnant female carrying an inbred fetus, which exclusively expresses the iLRP and not an unshared, non-cross protective TSTA [51].

Monomers of the 37-kDa iLRP that link with galectin-3 to form the 67-kDa mLRP in the plasma membrane have been described by others [26, 43, 52, 53].

The expression of mLRP in specialized adult mammalian cells following differentiation enables these cells to exhibit mobility through the laminin basement membranes present in adult tissues [26]. iLRP expressed in early fetal cells is immunogenic for the mother, but loses its immunogenicity near the middle of fetal development in both rodents and humans [35]. Is this the result of altered conformational expression of monomeric iLRP after acylation and dimerization in late fetal development, or altered antigen processing of the dimeric protein by maternal antigen-processing cells (APCs)? It could also be due to the inhibitory effect of galectin-3, either in its free or bound form as in mLRP, on the T-cell immune responses [23].

**Acknowledgments.** The authors wish to thank Mr. David B. Rizk of Tulane University for his excellent figure drawings and for formatting the references for this review.

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