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# Galectin signature in normal pregnancy and preeclampsia

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ABSTRACT

Members of the galectin family are expressed within the female reproductive tract and have been shown to be involved in multiple biological functions that support the progression of pregnancy. Specific expression patterns of different members of this family have been identified at the maternal decidua and on the placental side. In some cases, mechanisms by which galectins exert their functions have been delineated in adverse pregnancy outcomes. This review summarizes studies on galectins that have been documented to be important for pregnancy maintenance, either supporting the maternal adaptation to pregnancy or the placentation process. In addition, we focus our discussion on the role of galectins in preeclampsia, a specific life-threatening pregnancy disorder.



## 1. Introduction

Galectins are a family of lectins that regulate diverse biological functions such as cell–matrix and cell–cell interactions, cell proliferation, cell differentiation, cellular transformation, and apoptosis. Many members of the galectin family have been shown to be involved in multiple reproductive functions, mainly through their influence on (a) the maternal immune system, (b) processes associated with placentation, and (c) the endocrine-immune cross talk; driving the establishment and maintenance of pregnancy.

Together with other contributions in the present special issue on the "2012 Reunion Workshop on Preeclampsia", our article aims to emphasize the role of this family in reproductive medicine and discuss the meaning of their dysregulation in pathological gestations with special focus on preeclampsia. In addition, we discuss the means by which preeclampsia can potentially be predicted by "galectin patterns" even before the disease can become clinically diagnosable. Prior knowledge about preeclampsia and the application of appropriate prenatal care and management before the disease progresses to become life-threatening can largely minimize maternal mortality.

### 1.1. Galectins as multifunctional regulators during pregnancy

Galectins (gal) constitute an ancient and widespread family of proteins defined by a conserved sequence of approximately 130 amino acids within their carbohydrate recognition domains (CRDs) that confers them the ability to bind β-galactoside-rich glycoconjugates (Barondes et al., 1994). To date, the mammalian galectin family comprises 19 members, of which 13 are expressed in human tissues (Cooper, 2002). Based on the number and structural arrangement of their CRDs, these proteins are further classified into three groups: prototype, tandem-repeat and chimera-type galectins (Barondes et al., 1994) (Fig. 1a). Most galectins (i.e., gal-1, -2, -5, -7, -10, -13, -14, -15, -16, -17, -19) contain a single CRD that may homodimerize and are hence defined as prototype. Tandem-repeat galectins (gal-4, -6, -8, -9, -12) contain two homologous CRDs (which may differ in their carbohydrate-binding affinities) connected by a short linker sequence, conferring

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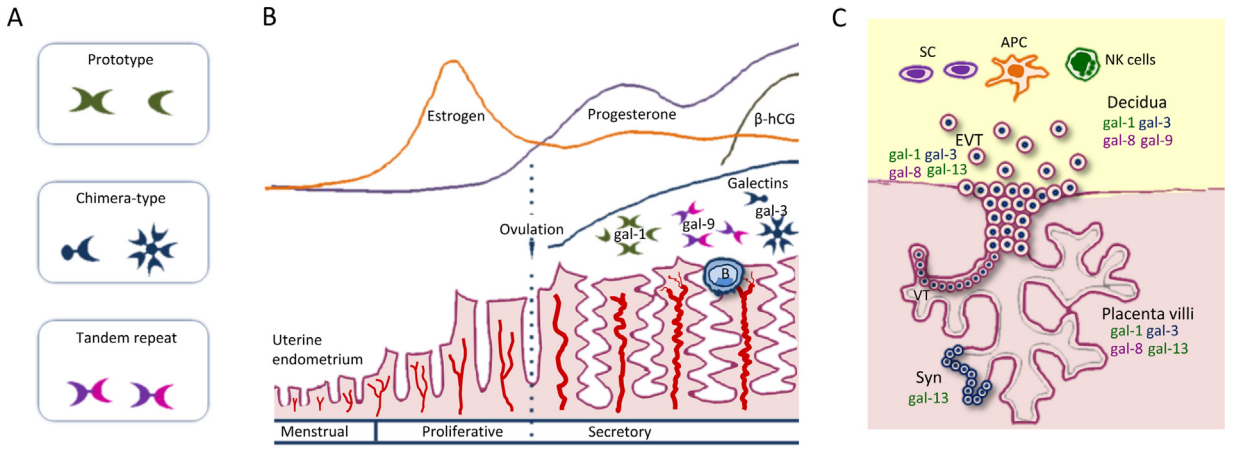


**Fig. 1.** Galectin expression following fertilization and early gestation. (A) Schematic diagram illustrating the different types of galectins. This family of lectins has been classified into three groups according to their structure: prototype, chimeric type, and tandem repeat galectins. The carbohydrate recognition domain (CRD) of most galectins is approximately 130 amino acids and is indicated here by the oval domain. (B) Pattern of galectin expression during the menstrual cycle and following fertilization. Galectins (gal-1, -3, and -9) are controlled by ovarian steroids, their expression peaking in stromal cells during the late secretory phase and further increasing in decidua after embryo implantation. Abbreviations: B, blastocyst; β-hCG, beta human chorionic gonadotropin. (C) Once pregnancy is established, galectins are differentially expressed at the maternal (decidua) and placental compartment. Abbreviations: gal, galectin; SC, stroma cells; APC, antigen-presenting cells (such as macrophages and dendritic cells); NK, natural killer cells; EVT, extravillous trophoblasts; VT, villous cytotrophoblasts; Syn, syncytiotrophoblast.

them multivalent binding activities. The only mammalian chimera-type galectin identified so far is gal-3, characterized by a C-terminal CRD and an N-terminal non-lectin domain of proline- and glycine-rich short tandem repeats, which are important for multimerization and cross-linking as well as for proteolytical regulation (Barondes et al., 1994; Brewer et al., 2002).

Galectins are found both in the intra- and extracellular milieus and display a unique combination of biological functions. Intracellularly, they engage in protein–protein interactions modulating various processes including cell growth, differentiation, survival, and migration (Liu et al., 2002). Some (i.e., gal-1, -3) have also been found to translocate to the nucleus and participate in transcriptional regulation and mRNA splicing (Hernandez and Baum, 2002; Liu et al., 2002). Though lacking a secretory signal sequence, galectins can also be exported from cells by non-classical secretion (Nickel, 2005) and mediate different responses by binding their carbohydrate ligands on cell-surface or ECM molecules (Brewer et al., 2002). Thus, 'secreted' galectins have been shown to influence cell adhesion, modulate apoptosis, and most importantly, function as cytokine-like molecules in the regulation of innate and adaptive immune responses (Hernandez and Baum, 2002; Rabinovich et al., 2007). Because of this functional polyvalence, galectins have recently become an appealing subject in the field of reproductive medicine, especially after the recognition of their pivotal role in immune-endocrine mechanisms governing the establishment and maintenance of pregnancy (Blois et al., 2007; Than et al., 2009; Tirado-Gonzalez et al., 2013).

### *1.2. Galectin expression at the fetal–maternal interface: where and what for?*

Studies profiling galectin expression in reproductive tissues have provided important insights into their role in pregnancy, highlighting the notion that a delicate interplay between maternal and fetal sources of expression appears to be critical for healthy gestations (Fig. 1b and c, Table 1). Thus, we here provide a brief description of the role of individual galectins expressed at the maternal–fetal interface in the establishment and maintenance of pregnancy.

#### *1.2.1. Galectin-1*

This prototypic galectin is one of the most abundantly expressed in the female reproductive tract, particularly in the endometrium/decidua (Von Wolff et al., 2005). Endometrial gal-1 expression is tightly controlled by ovarian steroids, peaking in stromal cells during the late secretory phase and further increasing in decidua. The spatiotemporal distribution of uterine gal-1 expression is similar in mice and humans, pointing to a possible role in blastocyst attachment and endometrial immune homeostasis during implantation (Choe et al., 1997; Von Wolff et al., 2005).

The pivotal role of gal-1 in feto-maternal tolerance was first demonstrated in a mouse model of stress-induced immunological abortion by showing that gal-1 supplementation substantially diminished fetal loss rates through the induction of tolerogenic dendritic cells (DC) and $CD4^+CD25^+IL\text{-}10^+$ Treg (Blois et al., 2007). Treatment with gal-1 additionally restored progesterone and progesterone-induced blocking factor (PIBF) serum levels in stressed animals, emphasizing the importance of a gal-1/progesterone synergistic pathway in the maintenance of pregnancy. Accordingly, it was recently shown that gal-1 rescues pregnancy in FK506-binding protein (fkbp)52 *knock-out* mice, which experience high fetal resorption rates due to progesterone resistance in the uterus (Hirota et al., 2012). Importantly, gal-1-expressing immune cell subsets, particularly NK cells, may also contribute to the tolerogenic decidual milieu during early pregnancy (Koopman et al., 2003; Kopcow et al., 2008). Human uterine

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**Table 1**
Summary of the functions and timing of expression of galectins during human pregnancies.

| Galectin | Function | Source | Timing of expression | Association with pregnancy disorders |
|---|---|---|---|---|
| gal-1 | Immune modulation, embryo implantation (?), angiogenesis? | Endometrium/decidua (stromal cells) | ↑Late secretory phase, ↑↑Decidua | ↓SA, ↑PE |
| | | uNK cells | Pre-implantation | ↓SA, ↑PE, ↑HELLP |
| | | Trophectoderm/ICM | ↑1st trimester | ↓SA |
| | | Placenta (VT, EVT) | ↑2nd trimester | |
| | | Serum/plasma | | |
| gal-3 | Immune modulation, embryo implantation (?), uNK cell regulation? | Endometrium/decidua (epithelium) | Peri-implantation period | |
| | | Placenta (VT, EVT) | Not described | ↑PE (EVT), ↑GTDs |
| | | Serum/plasma | | Unknown |
| gal-8 | ECM remodeling (?), angiogenesis? | Decidua (stromal cells, glands) Placenta (VT, EVT, Syn) | 1st trimester | Unknown |
| gal-9 | Immune modulation | Endometrium/decidua (epithelium) | ↑Decidualization | ↓SA (Lgals9 D5/10) |
| | | Placenta (VT) | 1st trimester | Unknown |
| gal-13 (PP13) | Immune modulation, arterial remodeling (?) | Placenta (Syn, endovascular trophoblasts) | | ↓PE |
| | | Serum/plasma | Detectable from 5 to 7 weeks | ↑PE (↓1st trimester), ↑HELLP |

Question marks (?) denote putative functions (not yet confirmed by experimental methods). Abbreviations: uNK, uterine natural killer; ICM, inner cell mass; VT, villous cytotrophoblast; EVT, extravillous trophoblast; Syn, syncytiotrophoblast; SA, spontaneous abortion; PE, preeclampsia; HELLP, GTD, gestational trophoblast disease; hemolysis elevated liver enzymes and low platelet syndrome. ↑ and ↓ denote increased/peak and decreased expression respectively.

NK cells, which represent ~70% of the decidual leukocyte infiltrate and play important roles in trophoblast invasion and vascular development (Moffett-King, 2002; Koopman et al., 2003), have been shown to promote apoptosis of activated maternal T cells due to up-regulated gal-1 expression (Kopcow et al., 2008). Since pathways controlling the accumulation and maturation of uNK cells appear to be largely dependent on progesterone signaling (Carlino et al., 2008; Kuang et al., 2010), it is conceivable that the proposed interplay between gal-1 and progesterone contributes to the immunomodulatory properties of NK cell subsets.

On the other hand, embryonic/placental expression of gal-1 seems to be important not only for immune evasion mechanisms, but also for developmental processes during implantation and placentation. For instance, gal-1 is expressed on the trophectoderm and inner cell mass of human pre-implantation stage embryos, where it may be involved in the attachment to the uterine epithelium (Tirado-Gonzalez et al., 2013). In the first-trimester placenta, gal-1 appears to play a significant role as a modulator of the invasive pathway of trophoblast differentiation, as indicated by its expression, mainly on extravillous trophoblasts (EVTs), and the finding that blocking gal-1 substantially abrogates migration in primary trophoblasts and HTR8/SVneo cells cultured in matrigel (Vicovac et al., 1998; Kolundzic et al., 2011a). Thus, in vitro studies have recently demonstrated that endogenous gal-1 influences the pattern of human leukocyte antigen (HLA)-G isoform expression in EVTs, indicating the important role of this lectin-linking invasion and tolerance induction mechanisms in trophoblast cells (Tirado-Gonzalez et al., 2013). Villous cytotrophoblasts (VTs), which undergo a fusion pathway of differentiation to form the syncytial outermost layer of the human placenta, also express gal-1, and this expression appears to be important for ECM organization and the modulation of maternal immune responses (Vicovac et al., 1998). For instance, proteomics studies have identified gal-1 as a VT-derived molecule with the ability to suppress T cell responses that is significantly downregulated in early pregnancy loss (Liu et al., 2006; Dong et al., 2008), supporting its importance in mechanisms promoting the maintenance of pregnancy. Finally, gal-1 expression is boosted under hypoxic conditions and a significant role for this lectin in tumor angiogenesis has been demonstrated in a variety of settings (Hsieh et al., 2008; Thijssen et al., 2010; Zhao et al., 2011). For instance, gal-1 can directly bind to neuropilin-1 (NRP-1) on endothelial cells (EC) and promote the NRP-1/vascular endothelial growth factor receptor-2 (VEGFR-2) signaling pathway, which is an important mediator of angiogenesis (Hsieh et al., 2008). Interestingly, expression of VEGFR-2 and NRP-1 becomes abundant during the peri-implantation period in mice (Halder et al., 2000), and inhibition of the VEGFR-2 signaling pathway provokes reduction of angiogenesis in the uterine decidua, with the subsequent disruption of pregnancy (Douglas et al., 2009). Although this possibility remains to be confirmed, it is conceivable that the relatively hypoxic milieu characteristic of the early maternal–fetal interface might contribute to gal-1 expression to support decidual and placental vascular development.

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*1.2.2. Galectin-3*

The expression of chimera-type gal-3 at the fetal–maternal interface partially overlaps that of gal-1 (Vicovac et al., 1998; Von Wolff et al., 2005), suggesting that an interplay between these lectins might be important for developmental processes and immune modulation during early pregnancy. Unlike gal-1, gal-3 is considered a pro-inflammatory signal targeting diverse innate immune components (i.e., macrophages, mast cells, and neutrophils) to promote their activation, degranulation, and cytokine production (Chen et al., 2005; Alves et al., 2010). Additionally, this lectin appears to play an important role in the modulation of adaptive immunity, as it has been shown that gal-3 can either promote or inhibit T cell apoptosis depending on its association with intracellular or extracellular binding partners (Yang et al., 1996; Stillman et al., 2006). Consistent with the proven antagonistic effects of gal-1 and gal-3 on T cell responses in vitro (Tribulatti et al., 2012), ovine placental gal-3 has been found to promote T-cell proliferation and activation (Iglesias et al., 1998).

In mice, uterine gal-3 expression is selectively upregulated during early stages of pregnancy and localizes to the luminal and glandular epithelia and the primary decidual zone, whereas at later stages this lectin is predominantly expressed in the placenta (Phillips et al., 1996). This distribution, together with the decreased implantation rates observed upon tissue-specific gal-3 knock-down in the uterus (Yang et al., 2012), indicates the pivotal role of this lectin during the embryo–maternal cross-talk driving implantation. Human gal-3 exhibits a similar spatio-temporal distribution during pregnancy, being upregulated in the endometrium at the peri-implantation period and detected in the placental VT and EVT lineages as gestation progresses (Maquoi et al., 1997; Von Wolff et al., 2005). Although extensively characterized in several species, the physiological functions of gal-3 expression at the fetal–maternal interface remain largely speculative. Interestingly, the above-described functional effects of gal-3 on innate immune components led to the suggestion of the possible role of this lectin in controlling uNK cell physiology (Phillips et al., 1996), a possibility that has been reinforced since the identification of cubilin as an endogenous gal-3 binding partner in mice (Crider-Pirkle et al., 2002). The latter study showed that while the main source of cubilin synthesis during pregnancy is the yolk sac epithelium, the protein is internalized in uNK perforin-containing granules, presumably via interactions with gal-3. The biological significance of this interaction remains to be determined, but it is anticipated that it may reflect mechanisms of fetal antigen processing or the modulation of uNK cytolytic potential.

*1.2.3. Galectin-8*

It was only recently that expression of the tandem-repeat lectin gal-8 was reported at the fetal–maternal interface (Kolundzic et al., 2011b); thus, its physiological role during pregnancy is rather speculative, based on functional observations in other settings.

Because gal-8 expression localizes to EVT columns, it is most likely to participate in ECM remodeling and as a physiological modulator of cell adhesion and migration during the invasive process. Indeed, gal-8 has been found to act either as a positive or negative regulator of adhesion by forming molecular complexes with integrins through carbohydrate–protein interactions (Zick et al., 2004). More recently, gal-8 has been identified as a binding partner of the hyaluronan receptor CD44 (Eshkar Sebban et al., 2007), which is also expressed at the fetal–maternal interface and seems to be important for tissue remodeling during mid to late gestation (Cordo-Russo et al., 2012). Interactions with integrins may additionally contribute to decidual immune trafficking and homeostasis, as demonstrated by the ability of gal-8 to induce leukocyte adhesion to endothelial cells and ECM components (Nishi et al., 2003; Yamamoto et al., 2008). Since gal-8 has also been involved in the regulation of T cell responses and angiogenesis (Cattaneo et al., 2011), it represents an attractive candidate for performing regulatory functions promoting the maintenance of pregnancy (Delgado et al., 2011).

*1.2.4. Galectin-9*

Owing to its unique influence on T cell survival and activation, tandem-repeat gal-9 is considered mainly an immunomodulatory galectin. Immune regulation mechanisms exerted by gal-9 largely depend upon interaction with its cell-surface receptor TIM-3, and include both stimulatory effects on macrophage and DC activation and immune suppression by promoting Th1 cell apoptosis (Zhu et al., 2011). Additionally, gal-9 can function as an anti-inflammatory signal promoting $Foxp3^+$ Treg and suppressing Th17 cell activity through TIM-3-independent mechanisms (Oomizu et al., 2012).

Endometrial gal-9 in humans is located mainly in epithelial cells and substantially upregulated in decidua (Popovici et al., 2005), concomitant with a possible role in dampening local immune responses. Indeed, it was further demonstrated that at least six gal-9 isoforms are expressed in human decidua, and that the *Lgals9 D5* variant can selectively suppress IFN-γ production by uNK cells (Heusschen et al., 2013). Consistent with these functions, we also demonstrated substantial anomalies in the pattern of decidual gal-9 isoform expression in a mouse model of spontaneous abortion and an association of decreased levels of the *Lgals9 D5/10* splice variant with human pregnancy loss (Heusschen et al., 2013). Finally, placental expression of gal-9 has also been reported in several species, though at lower levels than in the decidual compartment (Thijssen et al., 2008; Froehlich et al., 2012). The physiological significance of this expression awaits further investigation.

*1.2.5. Galectin-13*

Expression of this galectin is largely restricted to placental tissue, where it was originally described as placental protein 13 (PP13) (Than et al., 1999). Its unique pattern of expression, localizing to syncytiotrophoblasts and endovascular trophoblasts associated with decidual spiral arteries, suggests that it might play a role in trophoblast invasion and vascular remodeling during placentation (Than et al., 2004). Placental gal-13 is also regarded as an endogenous danger/damage signal, as its secretion from the syncytiotrophoblast is dramatically upregulated at the

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onset of preeclampsia and the HELLP (**H**emolysis **E**levated **L**iver enzymes and **L**ow **P**latelet) syndrome (Than et al., 2008a; Balogh et al., 2011). This lectin likely also plays an important role in feto-maternal tolerance, as it has been shown to promote apoptosis of activated T cells and macrophages (Than et al., 2009). Accordingly, gal-13 is selectively associated with T-cell-, neutrophil- and macrophage-containing decidual zones of necrosis (Kliman et al., 2012), suggesting that it might act to attract, activate, and kill maternal immune cells, and facilitate trophoblast invasion and conversion of the maternal spiral arterioles. As will be discussed later, decreased gal-13 expression may underlie the impaired trophoblast invasion and arterial remodeling typically observed in preeclampsia, highlighting the potential role of this lectin as a disease biomarker.

### 1.3. Preeclampsia, a life-threatening disease

Preeclampsia is a pregnancy-specific syndrome with an unknown etiology, defined by sudden onset hypertension (≥140 systolic/90 diastolic mmHg) and proteinuria (>300 mg/24 h) after 20 weeks of gestation (Lindheimer et al., 2009). Preeclampsia is responsible for significant maternal and fetal morbidity world-wide, also in the long-term increasing the risk of cardiovascular and metabolic (e.g., diabetes and obesity) disorders in mothers and newborns in later life (Sibai, 2006; Harskamp and Zeeman, 2007). Being a heterogeneous syndrome, preeclampsia may be classified based on the gestational age at delivery, as early-onset disease (<34 weeks) and late-onset disease (>34 weeks) (Von Dadelszen et al., 2003). It is widely accepted that early- and late-onset preeclampsia may be qualitatively different diseases with different original development (Huppertz, 2008). Although the placenta may play a crucial role in the development of both types of preeclampsia, the late-onset disease is believed to occur as a consequence of inadequate maternal adaptation to pregnancy, while the early-onset form is mainly associated with poor placentation. Indeed, early-onset preeclampsia differs from late-onset disease in many aspects (Staff et al., 2013), also in terms of immune cell function (Von Dadelszen et al., 2003) and cytokine levels (Vince et al., 1995). While late-onset disease is commonly associated with good maternal and perinatal outcomes, early-onset preeclampsia is usually a more severe condition, both for the mother and for the offspring, linked to a greater risk of recurrence in later pregnancies (Sibai et al., 1991) as well as future cardiovascular disease (Sibai, 2006; Harskamp and Zeeman, 2007). Although the pathogenesis of preeclampsia is still the subject of intensive research, Redman's group (Redman, 1992; Redman et al., 1999) developed a hypothesis to explain this syndrome as a "two-stage disease". Thus, the first stage occurs in early pregnancy where poor placentation results in placental hypoxia, causing no maternal symptoms. Later on, in the second stage, a systemic inflammatory response caused by the release of anti-angiogenic factors (such as sFlt-1, sEng) and inflammatory cytokines (e.g., IL-8, IL-6, and IL-1β) into the circulation by the oxidative stressed placenta leads to the signs and symptoms of preeclampsia (Sargent et al., 2007; Redman and Sargent, 2009, 2010; Powe et al., 2011; Herse et al., 2012). This two-stage disease theory has later been further developed into a "three-stage disease" (Redman and Sargent, 2010). Independent of the number of theoretical stages of preeclampsia development, identification of biomarkers during preclinical phases of preeclampsia could represent an important advantage for the clinicians to manage the syndrome and to target women for intensified follow-up and appropriate timing of delivery to optimize pregnancy outcome.

### 1.4. What do we know about galectins in preeclampsia?

So far, three members of the galectin family have been described to be deregulated in tissue derived from preeclamptic patients. The work done in this field is mainly descriptive and based on the evaluation of galectin expression in already diagnosed disease. Pioneer work from Jeschke's group (Jeschke et al., 2007) showed that gal-1 and gal-3 are up-regulated on the membrane of EVT in preeclampsia- and HELLP syndrome-derived placentas. In addition, the expression of gal-1 was up-regulated in decidual tissue of preeclamptic placentas and villous trophoblast tissue of HELLP placentas. This is in agreement with the subsequent work published by Romero's group, which described that gal-1 is overexpressed in patients with preeclampsia, both at the mRNA and at the protein level (Than et al., 2008b). The over-expression of placental gal-1 during late-onset preeclampsia could be attributed to the role of this lectin in immune regulation (Camby et al., 2006), since an exaggerated maternal inflammatory response is commonly observed in this disease (Redman et al., 1999). In this regard, we recently showed that maternal circulating gal-1-expressing T and NK cells are decreased in preeclampsia compared with normal pregnancy (Molvarec et al., 2011), supporting the notion that the lack of gal-1 could contribute to the excessive inflammatory response that characterizes this syndrome (Fig. 2). However, we found that circulating gal-1 serum levels in early- and late-onset preeclamptic women did not differ from those observed in normal gestation. Indeed, as gal-1 circulating levels reflect both maternal and placental expression of this lectin, the determination of gal-1 in maternal circulation once the preeclampsia is diagnosed may not provide further information about its role in this pregnancy disorder. Interestingly, the studies from Jeschke's and Romero's groups mainly analyzed patients during late-onset preeclampsia (>34 weeks) and in at least one of these studies the authors described samples included in the analysis originating from vaginal delivery. This is an important inclusion criterion that could influence the expression of galectin observed in preeclampsia, since uterine contractions and the oxidative stress associated with labor during vaginal delivery influences gene expression (Cindrova-Davies et al., 2007). Further studies need to be conducted, including a more homogeneous group of preeclampsia patients, maybe following the classification based on the time of delivery. It would also be important to assess circulating maternal gal-1 levels in a retrospective cohort of patients, which could provide new insights into the value of galectin as an early biomarker

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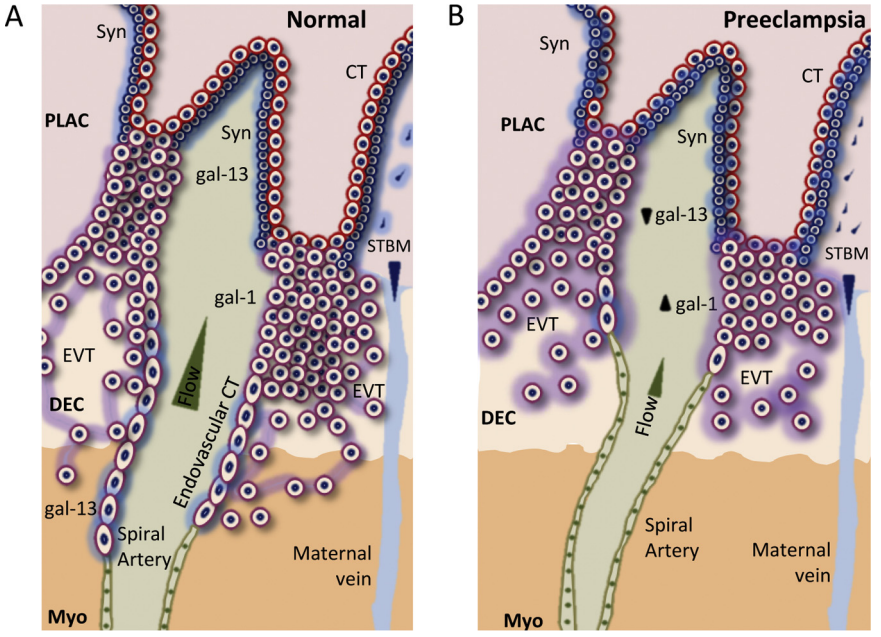


**Fig. 2.** Schematic representation of the galectin pattern expression during uneventful gestation and preeclampsia. (A) During normal pregnancy, galectins (gal-1 and gal-13) are expressed on trophoblast cells, regulating vital processes associated with adequate placentation, such as migration, invasion, and spiral artery remodeling. (B) When the preeclampsia syndrome develops, downregulation of gal-13 in Syn and endovascular CT is observed, linked to enhanced STBM shedding into the maternal circulation. In addition, gal-1 expression is upregulated, probably because of the excessive maternal inflammatory response. Abbreviations: PLAC, placenta; DEC, decidua; Myo, myometrium; EVT, extravillous trophoblasts; Syn, syncytiotrophoblast; STBM, syncytiotrophoblast-derived microparticles.

of the disease, improving treatments for this pregnancy-specific syndrome.

The third galectin that has been described to be deregulated during preeclampsia is gal-13/PP13. For instance, placental expression of mRNA and protein *Lgals13* is down-regulated in early and late-onset preeclampsia patients compared with control groups (Than et al., 2008a; Sammar et al., 2011). Furthermore, Than et al. found that cytoplasm protrusions, membrane blebs and shed membrane particles are rich in gal-13 expression (Than et al., 2008a). Although syncytiotrophoblast-derived microparticles (STBMs) are normally shed into the maternal circulation by the placenta during pregnancy, their levels are substantially increased during the preeclampsia syndrome (Redman and Sargent, 2008). Accordingly, maternal circulating gal-13 levels are increased in preterm preeclampsia and HELLP syndrome during the third trimester (Than et al., 2008a) (Fig. 2). The authors speculated that increased syncytiotrophoblastic shedding of gal-13 could be the major source of its increased maternal serum concentrations in early-onset preeclampsia, which is probably true since other brush border localized placental proteins (e.g., PP5/TFPI-2) are increased in the maternal circulation during the course of preeclampsia (Ogawa et al., 2007). In addition, there are at least three studies strengthening the concept that gal-13 could be considered an early indication of the development of preeclampsia. For instance, placental *Lgals13* mRNA levels were down-regulated in patients who subsequently developed preeclampsia (Sekizawa et al., 2009). When analyzing the cellular component of the maternal blood in a case-controlled study, Shimizu et al. found that *Lgals13* RNA expression in maternal peripheral blood samples was lower than in controls (Shimizu et al., 2009). Similar results were found by Farina et al. (2010), suggesting that the down-regulation of gal-13 during the first trimester could be the consequence of poor placentation, and therefore this lectin could emerge as a predictive factor for preeclampsia. This notion has been reinforced by the results of a recent meta-analysis covering 16 studies published between January 2006 and September 2012, which used currently available ELISA and Delfia immunoassays to evaluate maternal blood PP13 as a marker of preeclampsia (Huppertz et al., 2013). In summary, the meta-analysis indicated that blood PP13 is lower in the first trimester among women who will subsequently develop preeclampsia, and that combination with additional markers (i.e., PlGF, Doppler pulsatility index of uterine arteries) enhances its predictive value by increasing preeclampsia detection rates (Nicolaides et al., 2006; Wortelboer et al., 2010). These results have led the authors to speculate that replenishing PP13 during early pregnancy would represent an attractive strategy for the prevention and management of the disease, a possibility that requires considerably more research, especially in view of the scarce information available on PP13 effects during gestation in vivo. In this regard, a recent study analyzed the effects of PP13 on gravid rats, showing that continuous administration of human PP13 leads to a substantial reduction in arterial blood pressure accompanied by an increase in the heart rate, due to general arterial vasodilation and decreased peripheral resistance (Gizurarson et al., 2013). If the beneficial effects of PP13

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were further verified by in vitro and animal studies, PP13 replenishment may constitute an attractive strategy to test in future clinical studies on preeclampsia.

## 2. Future research and conclusion

Galectins regulate different processes associated with placentation and maternal adaptation to pregnancy, emerging as attractive candidates to be required for healthy gestation. Thus, the study of galectins during pregnancy is of huge importance since they seem to play a major role in different physiopathological settings. The variety of galectin-null mouse strains available to date (i.e., *Lgals1*, *Lgals3*, *Lgals8*) represents an instrumental tool for exploring galectin functions in reproduction, but unfortunately, studies providing an extensive characterization of these mice throughout pregnancy are still scarce. For instance, gal-1 knock-out mice were originally reported to have no overt reproductive phenotype; however, subsequent studies showed that the genetic deficiency of this lectin led to increased fetal loss rates in allogeneic pregnancies (Blois et al., 2007). Likewise, *Lgals3* and even *Lgals3/Lgals1* knockouts were generated more than ten years ago, but the information available on their reproductive performance is limited to the observation that implantation can still occur in the absence of these lectins (Colnot et al., 1998). Detailed examination of these animal models during physiological events, such as trophoblast differentiation, invasion and placental vascular development would be helpful in understanding the role of galectins during pregnancy complications. However, one caveat to the analysis of galectins during gestation is their promiscuous expression in both the maternal and placental compartments, limiting the interpretation of results. Dissecting their role during the maternal adaptation to pregnancy and placentation could represent the key to the development of new strategies to manage pregnancy complications and life-threatening disorders such as preeclampsia.

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