



Pregnancy Galectinology: Insights Into a Complex Network of Glycan Binding Proteins

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Galectins are a phylogenetically conserved family of soluble β -galactoside binding proteins, consisting of 15 different types, each with a specific function. Galectins contribute to placentation by regulating trophoblast development, migration, and invasion during early pregnancy. In addition, galectins are critical players regulating maternal immune tolerance to the embedded embryo. Recently, the role of galectins in angiogenesis during decidualization and in placenta formation has gained attention. Altered expression of galectins is associated with abnormal pregnancies and infertility. This review focuses on the role of galectins in pregnancy-associated processes and discusses the relevance of galectin-glycan interactions as potential therapeutic targets in pregnancy disorders.

Keywords: galectins, pregnancy, placentation, glycans, preeclampsia

INTRODUCTION

During pregnancy, a delicately regulated interplay of endocrine, immune and metabolic processes is established in order to sustain offspring development. The coordination of a series of simultaneous events occurring at both sides of the maternal-fetal interface, including multiple signaling pathways driving cell growth and differentiation, vascular development, and immune regulation, is critical for a successful pregnancy outcome. At the maternal site, complex immunoregulatory mechanisms support active tolerance of fetal alloantigens while also remaining competent to elicit an effective response toward pathogenic insults (1). Throughout pregnancy the uterine vascular bed experiences dramatic changes with extensive remodeling of existing vessels and formation of new networks through the process of angiogenesis (2), allowing for the proper delivery of oxygen and nutrients to the developing fetus. In parallel, at the fetal site, the process of placentation relies on a complex interaction between invasive trophoblasts and maternal immune cells involving developmentally regulated periods of branching angiogenesis, non-branching angiogenesis, trophoblast differentiation and syncytium formation. Disruption of this normal

pattern of placental development will directly impact placental function, with well-recognized consequences leading to suboptimal pregnancy outcomes (3).

The placenta sustains pregnancy by providing an immunological barrier between the mother and fetus, mediating the transfer of gases, nutrients and water and secreting a variety of hormones, cytokines, and signaling factors. As the active interface mediating maternal-fetal communication, the placenta plays a key role in sensing and modulating perturbations in the maternal environment and transmitting these stimuli to the developing fetus, with potential consequences in long-term offspring health. Indeed, it is now well-recognized that an adverse intrauterine environment during early development can modify disease predisposition in adult life as stated in the so-called “developmental origins of health and disease” or “fetal programming” paradigm. From the time of pioneer studies correlating birth weight and altered fetal growth with predisposition to chronic conditions as cardiovascular disease and diabetes (4), accumulating experimental evidence has contributed to the identification of multiple maternal constitutional and life style factors that can impact long-term individual health as well as the mechanisms involved in the transmission of these programming stimuli across the placenta (5–7).

Among the multiple mediators involved in pregnancy orchestration, the galectin family of β -galactoside binding proteins elicits great interest in the reproductive medicine field due to their unique ability to modulate diverse developmental processes and their potential use as biomarkers for gestational disorders. In this review we discuss the current knowledge on the role of galectins in supporting maternal adaptations to pregnancy and placental development, the impact of their dysregulation for development of disease and the potential application of galectinome profiling studies for diagnostic and therapeutic interventions in adverse pregnancy outcomes.

GENERAL ASPECTS OF GALECTINS

Complex carbohydrates on the cell surface and the extracellular matrix (ECM) encode abundant structural information that when decoded by specific carbohydrate-binding proteins (lectins) modulates interactions between cells, or cells and the ECM (8, 9). Based on their structural folds and canonical sequence motifs in the carbohydrate recognition domain (CRD), lectins have been organized into several families that include galectins (formerly S-type lectins), C-type, F-type, X-type, R-type, P-type, and several other families [Reviewed in (10)]. The taxonomic distribution of selected lectin families and their structural analysis have yielded critical information about their functional aspects and evolutionary history. While F- and C-type lectins—are largely heterogeneous and evolutionary diversified lectin families (11, 12), from a structural standpoint, galectins are relatively conserved (13, 14). Galectins are non-glycosylated soluble proteins characterized by a unique sequence motif in their CRDs and affinity for β -galactosides (13). Most galectins show preference for N-acetylated disaccharides such as N-acetyl-lactosamine (LacNAc; Gal β 1,4GlcNAc) and related

structures, whereas others have preference for blood group oligosaccharides (13–15).

Galectins are synthesized in the cytoplasm, and can be translocated into the nucleus where they can form part of the spliceosome (16, 17). Galectins can also be secreted to the extracellular space by non-classical mechanisms as they lack a typical signal peptide possibly by direct transport across the plasma membrane (18). Once secreted, galectins bind to carbohydrate ligands in the ECM and the cell surface, namely glycans that display LacNAc and polylectosamine chains [(Gal β 1, 4GlcNAc) $_n$] (13) (**Figure 1**). These include laminin and fibronectin, mucins, lysosome-associated membrane proteins, and numerous cell surface glycoproteins (19–22). Among the latter, galectins bind with high affinity to glycosylated cell surface signaling molecules such as α and β integrins (21) and the signaling mucin MUC1 (22). Integrins are the predominant laminin and fibronectin-binding proteins expressed on differentiating cells and represent important ligands for galectins involved in cell adhesion, motility and differentiation (21–24). For some galectins, the immediate binding to ligands in the oxidative extracellular environment is key to the stability of their carbohydrate-binding activity (25). The crystal structure of galectin-1 (Lgals1) revealed six key cysteine residues, some of which are located on the surface of the molecule on the face opposite to the CRD and are potentially susceptible to oxidation (26–28). Under non-reducing conditions, intramolecular disulfide bridges are formed resulting in conformational changes that preclude Lgals1 from forming a dimer (29). A critical interplay takes place between the oxidation state of cysteine sulfhydryl groups and the ligand binding and dimerization equilibrium, suggesting that specific binding to glycan ligands enhances dimerization and reduces sensitivity to oxidative inactivation (25). In addition, extracellular galectins can also recognize exogenous ligands, such as glycans on the surface of viruses, bacterial pathogens and parasites (30–33), a hallmark of other lectin types, such as C-type lectins (11). Furthermore, galectin secretion into the extracellular space upon stress has been proposed to constitute non-infectious “danger signals” that can initiate or exacerbate inflammatory responses (34).

STRUCTURAL ASPECTS OF GALECTINS

Galectins are characterized by their extensive taxonomic distribution and striking evolutionary conservation of primary structures, gene organization, and structural fold (11). The identification of galectin-like proteins in the fungus *Coprinosia cinerea* (35) and in the sponge *Geodia cydonium* (36) revealed structural conservation of galectins in eukaryotic evolution. Furthermore, proteins sharing the galectin structural fold identified in the protozoan parasite *Toxoplasma gondii* (37, 38) and in rotaviruses (39–41) suggest either early emergence of the galectin fold or horizontal transfer from the vertebrate hosts, respectively. In general, galectin polypeptide subunits exhibit a relatively simple domain organization, housing one, two, or four galectin CRDs (11).

Although galectins have been evolutionarily conserved (42), the galectin repertoire in any given mammalian species is

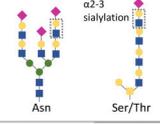
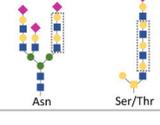
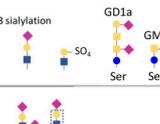
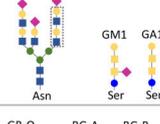
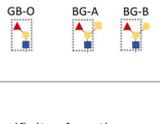
Galectin	Classification	Glycan specificity	Source of expression	Function	Dysregulation in pregnancy disorders
gal-1 	Prototype One CRD, which can dimerize		Endometrium/ decidua (stromal cells), uNK cells Trophoblast/ICM Placenta (VT, EVT)	Immune modulation, embryo implantation, trophoblast invasion, angiogenesis	Placenta expression: ↑ GDM, ↓ early onset PE, ↑ late onset PE, ↑ HELLP, ↓ SA Systemic levels: ↓ GDM, ↑ late onset PE, ↓ SA
gal-3 	Chimera One CRD fused with a non-lectin domain		Endometrium/ decidua (epithelium), Placenta (VT, EVT)	Immune modulation, embryo implantation, uNK cell regulation?	Placenta expression: ↓ IUGR, ↑ PE, ↑ HELLP, ↑ GTDs Systemic levels: unknown
gal-8 	Tandem-repeat Two different CRD		Decidua (stromal cells, glands) Placenta (VT, EVT, Syn)	ECM remodeling?, angiogenesis?, immune modulation?	Placenta expression: ↓ IUGR (gender specific) Systemic levels: unknown
gal-9 	Tandem-repeat Two different CRD		Endothelium/decidua (Epithelium) Placenta (VT)	Immune modulation	Placenta expression: ↓ SA (Lgals9 D5/10), ↑/↓ IUGR (gender specific), ↑ PE Systemic levels: ↓ SA
gal-13 (PP13) 	Prototype One CRD, which can dimerize		Placenta (Syn, endovascular trophoblasts)	Immune modulation, Arterial remodeling and vasodilation	Placenta expression: ↓ PE, ↓ GDM Systemic levels: ↑ PE (↓ 1st trimester), ↑ HELLP, ↑ GDM

FIGURE 1 | Summary of galectins' glycan specificity, functions and sources of expression in mammalian pregnancies. Question marks (?) denote putative functions (not yet experimentally confirmed in the context of pregnancy). BG, blood group; uNK, uterine natural killer; ICM, inner cell mass; VT, villous cytotrophoblast; EVT, extravillous trophoblast; Syn, syncytiotrophoblast; GDM, gestational *diabetes mellitus*; SA, spontaneous abortion; PE, preeclampsia; HELLP, hemolysis elevated liver enzymes and low platelet syndrome; GTD, gestational trophoblastic disease; IUGR, intrauterine growth restriction. ↑ and ↓ denote increased/peak and decreased expression, respectively. ● Mannose ● Galactose ■ N-acetylglucosamine ■ N-acetylgalactosamine ◆ Sialic Acid ▲ Fucose.

constituted by multiple galectin types, subtypes, and isoforms (13). Based on the CRD organization of the polypeptide monomer, mammalian galectins (and by extension, galectins in all vertebrate taxa) have been classified in three major types: “proto,” “chimera,” and “tandem-repeat” (TR) types (43) (Figure 1). Proto-type galectins contain one CRD per subunit and can form concentration-dependent non-covalently linked homodimers. Dimerization of proto-type galectins is key to their function in mediating cell-cell or cell-ECM interactions (44, 45). Two Lgals1 monomers interact via amino acid residues from a hydrophobic core that establish a dimerization equilibrium with a Kd of 7 μ M (16). Both proto- and TR-type galectins comprise several distinct subtypes, all numbered in the order of their discovery, while chimera galectins include a single subtype (13). Lgals1, -2, -5, -7, -10, -11, -13, -14, and -15, are included in the proto-type. Chimera-type galectins, represented by Lgals3, have a C-terminal CRD and a proline- and glycine-rich N-terminal “tail.” Ligand-driven interactions of Lgals3 subunits via the N-terminal domain mediate their oligomerization into trimers and pentamers (46). TR galectins display two similar—albeit not identical—CRDs connected by a functional linker peptide (47), and comprise the Lgals4, -6, -8, -9, and -12 subtypes. Galectin subtypes may be expressed as multiple isoforms in a single cell type or as tissue-specific variants generated by alternative splicing (13, 48), positive selection, and amino acid replacements in carbohydrate-recognition domains (49). Among the proto, chimera and TR galectin types, several

subtypes, that include human Lgals1, Lgals2, Lgals3, Lgals9, and three galectins that cluster in the human chromosome 19 [Lgals13 (pp. 13), -14, and -16], have been recently investigated with regards to their potential roles in fertilization, embryo implantation, placentation, and the various stages of normal and pathological pregnancy (49–52).

The structural fold of Lgals1 and the amino acid residues of the CRD that directly or indirectly—via water molecules—interact with the hydroxyl groups on the carbohydrate ligands have been identified by the resolution of the crystal structure of the Lgals1/LacNAc complex (26, 27, 53). The Lgals1 subunit is a β -sandwich consisting of a 135 amino acid-long polypeptide that folds into two antiparallel β -sheets of five and six strands each (S1–S6 and F1–F5). This globular structure contains one carbohydrate binding cleft formed by three continuous concave strands (S4–S6) that includes all amino acid residues that interact with LacNAc and are responsible for the carbohydrate specificity of Lgals1: histidine 44, asparagine 46, arginine 48, histidine 52, asparagine 61, tryptophan 68, glutamic acid 71, and arginine 73 (27). Tryptophan 68 establishes a hydrophobic stacking interaction with the non-reducing terminal galactose ring. Additional water-mediated interactions between His52, Asp54, and Arg73 in the Lgals1 CRD with the nitrogen of the NAc group rationalize the higher affinity for LacNAc over lactose. The rigorous assessment of the galectins' carbohydrate-binding affinity has been enabled by biophysical approaches, such as

microcalorimetry measurements and surface plasmon resonance analysis. For example, the dissociation constants of bovine Lgals1 for Lac, LacNAc, and thiodigalactoside measured by microcalorimetry were in the range of 10^{-5} M, with two binding sites per Lgals1 dimer (54). The overall structure of the Lgals3 CRD is very similar to the Lgals1 CRD although in the former the carbohydrate-binding site is shaped as a cleft open at both ends, exposing the GlcNAc of the LacNAc to the solvent (55). This extended binding site in Lgals3 results in increased affinity for polylectosamines and for ABH blood group oligosaccharides [Fu α 1, 2; GalNAc α 1,3(Fu α 1,2); and Gal α 1,3(Fu α 1,2)] (55). The structures of the individual N- and C-terminal CRDs of TR galectins, such as galectins-4, -8, and -9, have been resolved by either crystallization or NMR spectroscopy. Results have shown that the two CRDs in the same galectin molecule are structurally similar but exhibit either different affinities for the same ligand such as observed in Lgals4, or different fold and specificities altogether, such as reported for Lgals8 (56–58).

Based on analysis of the galectin primary structure and intron-exon position in various vertebrate species it has been proposed that along the vertebrate lineages leading to mammals, galectins evolved by duplication of a primordial single CRD galectin gene that produced a bi-CRD gene, with the N- and C-terminal CRDs later diverging into two subtypes (F4-CRD and F3-CRD) of distinct exon-intron organization. Single-CRD galectins display the F3- (e.g., Lgals1, -2, -3, -5) or F4- (e.g., Lgals7, -10, -13, -14) subtypes, while TR galectins display both F4 and F3 subtypes (Lgals4, -6, -8, -9, and -12) (13, 42). In invertebrate species, galectins exhibit one, two, or four tandem-arrayed CRDs (59–61). In those invertebrate galectins that carry multiple CRDs, these are structurally similar but not identical, suggesting that they differ in their fine carbohydrate specificity (61). How the multiple CRD galectins from invertebrates relate to the vertebrate TR galectins remains to be fully understood, but a preliminary phylogenetic analysis revealed that individual CRDs of a four-CRD galectin clusters with the mammalian single CRD galectins rather with the TR galectins, suggesting that this gene is the product of two consecutive duplications of a single-CRD galectin gene (61).

FUNCTIONAL ASPECTS OF GALECTINS

As discussed above, TR galectins display two CRDs in a single polypeptide, that can interact with and cross-link multivalent ligands, either soluble glycoproteins or glycolipids, or ECM and complex glycans on the cell surface. Although proto- and chimera-type galectin subunits possess a single CRD, they can organize as oligomeric structures that also bind multivalent ligands with increased avidity (44, 45). The density of the cell surface glycans and their scaffolding (as glycoproteins, glycolipids or polysaccharides) modulates affinity of the CRD-ligand interaction via negative co-operativity (45), and can lead to ligand cross-linking, and formation of lattices that cluster these ligands into lipid raft microdomains (44). These interactions can promote reorganization or

association of cell surface components, regulate turnover of endocytic receptors, activate or attenuate signaling pathways, and in turn, modulate cell function (44). Further, because galectin types and subtypes exhibit notable differences in carbohydrate specificity and affinity and bind a broad range of glycans that display the requisite topologies, the galectin repertoire displays considerable diversity in recognition properties that together with their distinct and unique tissue distribution and local concentrations, supports extensive functional diversification (13, 30). Thus, the biological function of a particular galectin may vary among cells, tissues and fluids, depending on their concentration, the availability and multivalent presentation of suitable carbohydrate ligands, and the redox properties of any particular intra- or extracellular microenvironment (30).

EARLY DEVELOPMENT AND TISSUE REGENERATION

The initial description in the early “80s of developmentally-regulated galectins in chicken muscle suggested that their biological roles were related to embryogenesis and early development. Further, the finding that chicken galectins preferentially recognized the abundant polylectosamines present on the myoblast surface and the ECM, suggested that galectins mediate myoblast fusion [reviewed in (14)]. Later studies suggested roles of murine Lgals1 and Lgals3 in notochord development and somitogenesis, and in skeletal muscle and central nervous system development (62, 63). In recent years, the increasing availability of null mice for selected galectins enabled their developmental phenotypic analysis. Although the phenotypes identified have been in some cases rather subtle, which hindered a rigorous assignment of the galectins’ biological roles, the use of galectin deficient models and tissue-specific knockouts is one of the most complete available tools for the analysis of the biological role of galectins. In addition, rodents express a complex galectin repertoire; this was attributed to functional redundancy of the multiple galectin types and subtypes. However, as the binding properties and natural ligands of each galectin have been rigorously characterized in recent years, it has become clear that this is not the case, and their unique biological roles are being elucidated in increasing detail. In the past few years, *Drosophila*, *C. elegans*, and zebrafish (*Danio rerio*) have become useful model systems to address the biological roles of galectins (64–68). For example, antisense knockdown approaches in zebrafish embryos for a Lgals1 isoform (Drgal1-L2) revealed a key role in differentiation and development of the myotome (69). The zebrafish model was also useful to assess the roles of galectins in tissue repair and regeneration (53, 70). Experimentally light-induced retinal injury in adult zebrafish was used in combination with an antisense knockdown approach to demonstrate that photoreceptor cell death upregulates expression and secretion of DrGal1-L2 by stem cells and neuronal progenitors in the Müller glia, and selectively regulates the regeneration of rod photoreceptors (70).

GENOME ORGANIZATION OF GALECTIN FAMILY MEMBERS

While galectins are usually grouped based on their architecture, a potential relationship between gene location and function has been investigated (42, 50). Genes encoding *Lgals1* and *Lgals2*, named *LGALS* in humans and *Lgals* in mice and other chordates, map to syntenic regions of chromosome 22 and chromosome 15, in humans and mice, respectively. Studies of the promoter sequences and expression of murine *Lgals1*, -2 and -7 revealed significant differences in the proximal promoter regions for putative transcription factor binding sites in these genes, which is believed to correlate with the ubiquitous gene expression of *Lgals1* and a more restricted expression of *Lgals2* and *Lgals7* (71).

Members of the human galectin gene family are found in different chromosomes, including chromosome 1, 11, 14, 17, 19, and 22. Than et al. proposed that some of the human galectin genes clustered in chromosome 19 and expressed in villous trophoblasts, including *LGALS13*, *LGALS14*, *LGALS16*, are developmentally regulated by DNA methylation and induced by transcription factors that drive villous trophoblast differentiation and trophoblast-specific gene expression (49). In addition, dysregulation of these galectin genes with a potential role in immune tolerance to the semi-allogeneic fetus was proposed to be associated with preeclampsia (49).

Interestingly, the *Lgals3* gene is different from other galectin genes in which gene duplication and inversion within a cluster has been reported. A single member has been identified per species hinting at a conserved function of *Lgals3* during evolution (42). In addition, *LGALS3* contains an internal gene, which is much less abundant than *LGALS3* transcripts and is expressed mostly in peripheral blood leukocytes producing an entirely distinct protein from *Lgals3* (72).

ROLE OF GALECTINS IN PREGNANCY ASSOCIATED PROCESSES

Expression profiling studies in reproductive tissues have shed important insights on the biological roles played by galectins in pregnancy orchestration, highlighting the importance of a delicate interplay between maternal and fetal sources of galectin expression for healthy outcomes (Figure 1). The following section provides a brief overview of the role of individual galectins expressed at the maternal-fetal interface in the establishment and maintenance of pregnancy.

GALECTIN-1 (LGALS1)

The functions of *Lgals1* in the context of pregnancy are the best characterized when compared to other members of the galectin family (Figure 1), likely due to its high level of expression by decidual stromal cells and trophoblast cell populations which suggested an important function (73). Indeed, *Lgals1* has been shown to play a role in a variety of biological processes highly relevant for pregnancy orchestration including angiogenesis, immune response regulation, cell adhesion, invasion, and

cell cycle progression through intracellular or extracellular mechanisms (23, 74–76).

Lgals1 expression is observed in 3–5 days human embryos potentially increasing trophoblast attachment to the uterine epithelium (77). After embryo attachment as the trophoblast layer differentiates, *Lgals1* localizes to villous cytotrophoblast where it may play a role in promoting syncytium formation, although this function has only been studied *in vitro* using the BeWo trophoblast tumor cell line (78, 79). More recently, *Lgals1* has been demonstrated to drive the differentiation of mouse trophoblast stem (TS) cells *in vitro*, by enhancing cell migration and invasiveness associated with a shift in the expression of matrix metalloproteinases, epithelial-mesenchymal transition markers and the TGF- β signaling pathway (80). Circulating levels of *Lgals1* increase significantly during pregnancy and several studies indicate the potential use of *Lgals1* as a biomarker for miscarriage, recurrent fetal loss and preeclampsia (PE) (77, 81–84). Whether circulating *Lgals1* retains carbohydrate-binding activity within the oxidative nature of the extracellular environment remains unknown as *Lgals1* exhibits exquisite sensitivity to oxidative inactivation (25, 85). In addition, a further question regarding concentration of galectins in serum or plasma is whether high picomolar concentrations are sufficient for galectins to act at a distance similar to circulating hormones (86). In this regard, some galectin-mediated cellular activities (e.g., *Lgals3* and *Lgals7*) (87, 88) might be sufficiently sensitive to be elicited by serum levels of galectins.

Lgals1 is highly expressed in the most invasive trophoblast cells of the placenta and membrane bound *Lgals1* has been proposed to regulate migration of primary trophoblasts and of an extravillous trophoblast (EVT) cell line (77, 89–91). Modulation of EVT migration by *Lgals1* could be related to its interaction with the $\beta 1$ integrin chain on the EVT membrane (90, 92–94, 94). Another reported ligand for *Lgals1* on the EVT membrane is the mucin *MUC1* (95). Expression of *MUC1* is increased during placental development and was found to be elevated in severe pre-eclamptic placentas (96) although the significance of this finding is unclear as *MUC1* has been shown to have adhesive and anti-adhesive properties (97). Interestingly, adhesion and invasion of the HTR-8 SV/neo EVT cell line to ECM components is negatively affected by *MUC1* overexpression (98). In endothelial cells, the membrane protein neuropilin-1 was identified as a ligand for *Lgals1* and the expression of neuropilin-1 in decidual cells, intermediate trophoblasts, and syncytiotrophoblasts has been recently reported (99, 100). The potential interaction of *Lgals1* with neuropilin-1 in these placental cells could potentially have functional consequences for placentation. As stated above, besides interacting with glycoproteins on the cell membrane, *Lgals1* interacts with glycoproteins deposited in the ECM and has been shown to have both anti-adhesive as well as pro-adhesive extracellular functions (23). In the placental ECM, *Lgals1* ligands include fibronectin, laminin, and osteopontin, which are also integrin ligands (19, 101–104).

The importance of *Lgals1* as a contributor to fetomaternal tolerance has been described by many investigators and has been extensively reviewed (51). Several immune cells with essential

roles in the establishment and maintenance of pregnancy synthesize and respond to Lgals1, e.g., CD4⁺ CD25⁺ regulatory T-cells, which play a very important role in tolerating the immunogenic paternal alloantigens (83, 105–110). In addition, *in vitro* studies showed that Lgals1 regulates the expression of human leucocyte antigen (HLA-G) in EVT cells demonstrating that Lgals1 contributes to tolerance via its interaction with immune and trophoblast cells (77).

GALECTIN-2 (LGALS2)

Lgals2 is predominantly expressed in the gastrointestinal tract and has been identified as one of the main gastric mucosal proteins proposed to have a protective role in the stomach by interacting with mucins (111). In addition, immune functions of Lgals2 have been proposed including its ability to induce apoptosis in activated CD8⁺ T-cells and its effects on monocytes (112, 113). Lgals2 was shown to polarize monocytes and macrophages to a pro-inflammatory, non-arteriogenic M1 phenotype, and reduce monocyte motility. Interestingly, Lgals2 regulation of monocyte/macrophage phenotype were attributed to its interaction with the lipopolysaccharide-binding protein CD14 in a non-carbohydrate dependent manner (112, 113). Lgals2 expression in the placenta was reported in both VT and EVT cells and was shown to be expressed at higher levels in VT and EVT of male compared to female placentas. Interestingly, in cases of intrauterine growth restriction (IUGR), there was no change in expression in female placentas compared to controls; however, expression of Lgals2 in male IUGR placentas was reported to be decreased compared to controls (114). While these studies should be repeated with a larger sample number, they may serve to caution investigators for the need to take the gender of the fetus into account as an important variable when analyzing possible changes in galectin expression when comparing normal to pathologic pregnancies. In addition, *Lgals2* expression was decreased in third-trimester EVT trophoblast cells in cases of PE on the protein and mRNA level (115) and also significantly down-regulated in the VT and EVT trophoblast of spontaneous and recurrent abortion placentas (116).

GALECTIN-3 (LGALS3)

Lgals3 has been implicated in the regulation of innate and adaptive immune responses, where it participates in the activation or differentiation of immune cells and contributes to phagocytic clearance of microorganisms and apoptotic cells by macrophages (117, 118). Lgals3 has been reported to promote but also to inhibit T-cell apoptosis depending on whether it binds to glycoproteins on the cell surface (CD45 and CD71) or to intracellular ligands (Bcl-2) (119, 120). In the placenta, Lgals3 was detected in all trophoblastic lineages including villous cytotrophoblasts (CTB) and EVT with a reduction of Lgals3 expression observed from the VT to the trophoblastic cell columns (121). This pattern of Lgals3 expression correlates with the switch from a proliferative to a migratory trophoblast phenotype and while placental

Lgals3 dysregulation has been associated with some obstetric complications including spontaneous or recurrent miscarriages, further studies are needed to understand its contribution to trophoblast biology (81, 122). In addition to trophoblasts, Lgals3 is expressed by maternal decidual cells (73). While showing a different expression pattern, both Lgals1 and Lgals3 have been proposed to play a role in cell-cell and cell-matrix interactions of trophoblast during placentation (121). Studies of the importance of Lgals3 in murine pregnancy by Yang et al. indicate that Lgals3 is expressed in the luminal and glandular epithelium and that an increase in Lgals3 is required for proper embryo implantation (123). In addition, Lgals3 affects chemotaxis and morphology of endothelial cells and stimulates capillary tube formation and angiogenesis *in vivo* (124). Therefore, besides its proposed roles in embryo implantation, immune regulation and trophoblast-matrix interactions, Lgals3 has a potential role in placental angiogenesis. It must be noted, however, that despite considerable research efforts over the past years, the precise physiological relevance of this lectin during pregnancy remains ill-defined. Comprehensive analysis of the placental phenotype, the regulation of vascular development and maternal adaptations in *Lgals3* deficient models could greatly aid our understanding of this lectin's role in pregnancy orchestration.

GALECTIN-7 (LGALS7)

Lgals7 is produced by the premenstrual and menstrual endometrial luminal and glandular epithelium, where it accumulates in menstrual fluid and has been proposed to act as a paracrine factor to facilitate post-menstrual endometrial re-epithelialization (125). While *Lgals7* mRNA was not detected in term placenta by real time-PCR, using immunohistochemistry, expression of Lgals7 was reported in the syncytiotrophoblast (STB), EVT and glandular epithelium in first trimester placenta, decidua and in the STB and endothelial cells of normal term placenta (50, 126). Menkhorst et al. suggested that Lgals7 may facilitate adhesion of the embryo to the endometrium and reported that the serum concentration of Lgals7 was significantly elevated in women (weeks 10–12 and 17–20) who subsequently developed PE compared to women with healthy pregnancies (126, 127). Another study, also explored the potential value of Lgals7 measurement as a biomarker and indicated that maternal serum Lgals7 levels had no value to predict the risk of spontaneous abortion (128). Clearly, further studies are required to confirm the expression of Lgals7 in placental cells and the potential usefulness of Lgals7 measurements in maternal serum as a biomarker for pregnancy pathologies should be evaluated with larger patient cohorts.

GALECTIN-8 (LGALS8)

Lgals8 is ubiquitously expressed and analysis of its expression in normal first trimester placentas indicated that *Lgals8* is expressed by VT and EVT, and is highly expressed in decidual stromal cells (129). Lgals8 has been referred to as an “angiogenesis regulator” in vascular and lymphatic endothelium by binding to

podoplanin in lymphatic vessels and CD166 (ALCAM, activated leukocyte cell adhesion molecule) in vascular endothelial cells (130). The role of this galectin in placental angiogenesis has not been explored but an initial report indicates that Lgals8 is not expressed in the endothelium of the placenta (130). The human gene (*LGALS8*) encodes seven different isoforms resulting from alternative splicing but the functional consequences of *Lgals8* splicing are poorly understood (130). Pro-inflammatory and immunosuppressive functions have been both attributed to this galectin in different experimental systems but so far, no studies on its possible role as an immunomodulator during pregnancy have been reported (131–135). Potentially, Lgals8 could play a role in trophoblast cell adhesion and migration as was reported in other cell types, but experimental evidence for the regulation of trophoblast function by this lectin is also lacking (136).

GALECTIN-9 (LGALS9)

The tandem-repeat Lgals9 has been implicated in immune regulation through binding to TIM-3, CD44 and the cell surface protein disulfide isomerase (PDI) (137–139). This galectin is expressed by many cell types including epithelial cells of the endometrium, trophoblasts, stromal cells of the decidua, endothelial cells including those in the placenta, and several types of immune cells (140–143). Splice variants of *Lgals9* have been reported with six of them expressed in human decidua, which may differ in their biological functions (143–145).

Compared to non-pregnant individuals, regulatory T cells show higher level of *Lgals9* expression as pregnancy proceeds and the level of Lgals9 in serum is significantly higher in women with normal pregnancies compared to post-partum and non-pregnant female controls (146). Interestingly, the serum levels of Lgals9 in pregnancy varied with the gender of the fetus as was also reported for some inflammatory cytokines and pro-angiogenic factors; Lgals9 is further increased in the serum of women carrying a male compared to a female fetus (147, 148). Li et al. proposed that Lgals9 contributes to the generation of CD25⁺ FoxP3⁺ T regulatory cells in -circulation and in the spleen and that engagement of Tim-3 by Lgals9 in peripheral NK cells facilitates the immunosuppressive activity of these cells during the first trimester of pregnancy (149). Additionally, they report that the concentration of Lgals9 in the plasma of women with normal pregnancies is significantly higher from that in women suffering from recurrent miscarriages but caution should be taken as the sample size was small and fetal gender was not considered in these studies (149).

Recently, lower levels of Lgals9 expression analyzed by immunohistochemistry were described in trophoblasts of the DBA/2-mated CBA/J mouse model of spontaneous abortion/PE when compared to normal CBA/J × BALB/c matings, further showing that Lgals9 blockade promoted a significant imbalance of Th1/Th2 immunity in this model (150). Additionally, altered placental Lgals9 expression together with dysregulated Tim-3 signaling in distinct NK and T cell subsets have been suggested to mediate the abortifacient effects of mifepristone in mouse pregnancies (151). Furthermore, activation of Tim-3/Lgals9

signaling pathway promotes decidual macrophages polarization to M2 subtype, alleviating the PE-like syndrome induced by LPS in a rat model (152). In conclusion, while a role for Lgals9 in immune tolerance during pregnancy has been reported by a handful of investigators, more studies considering splice variants, fetal gender, and Lgals9 receptors on target cells are required to better understand the potential role for this galectin as a contributor of the systemic and local immune regulation during pregnancy.

GALECTIN-10 (LGALS10)

Prototype Lgals10, also known as eosinophil Charcot-Leyden crystal protein, appears to play an important role in the differentiation of neutrophils and the functional properties of CD25⁺Treg cells (153, 154). Subsequently, expression of this lectin at the maternal-fetal interface has been described mainly in the STB and to a smaller extent in the decidua during the first trimester, showing decreased levels in spontaneous abortion patients (116, 155). The precise physiological role played by this lectin in pregnancy is still unknown but interestingly, its expression is driven from a chromosome 19 gene cluster comprising also galectins -13, -14, -16, and -17, which emerged during primate evolution as a result of duplication and rearrangement of genes via a birth-and-death process (49, 50). Galectins in the chromosome 19 cluster show primarily placental expression and may be involved in the regulation of unique pregnancy associated processes, including maternal immune tolerance and villous trophoblast differentiation (49, 50, 156).

GALECTIN 13 (LGALS13)

Lgals13 is also known as placental protein 13 (PP13) and was first isolated from human placenta (157). This galectin is predominantly expressed by STB cells of the placenta, in which nuclear staining and strong labeling of the brush border membrane is observed (158, 159). Although originally reported to be absent in serum of pregnant women, Lgals13 is detected in increasing concentration in maternal serum as pregnancy progresses becoming undetectable 2–5 weeks post-partum (158, 160, 161). Besides being found in a soluble form in circulation, Lgals13 is also located inside and on all types of STB-derived extracellular vesicles (162).

Lgals13 has been proposed to have immune regulatory functions, and in studies in rodents it has been shown to reduce blood pressure associated with activation of endothelial prostaglandin and nitric oxide signaling pathways (163–166). The potential for Lgals13 as a useful biomarker for PE has been suggested by Burger and co-workers. They reported that in the 1st trimester, lower than normal Lgals13 levels were found in IUGR and PE, particularly in the early-onset form. In the 2nd and 3rd trimesters, higher than normal concentrations were found in PE, IUGR and in preterm delivery (PTD) (160). On the other hand, lower placental *Lgals13* mRNA and protein expression were found in preterm PE and HELLP syndrome, although the immunoreactivity of the STB microvillous membrane was

reported to be stronger in these pregnancies than in age-matched controls suggesting increased membrane shedding (167). The usefulness of Lgals13 as a biomarker for PE has been questioned as late second-trimester Lgals13 alone does not increase the ability to predict PE when compared to second-trimester Doppler pulsatility index and other potential biochemical markers (168), highlighting the need to consider the interactions between different signaling pathways in disease pathogenesis when in search for sensitive, reliable biomarkers. In this regard, recent studies suggest that the kinetics of Lgals13 expression in PE would result from the concerted actions of this protein and antiangiogenic factors as sFlt-1 on the maternal vascular system, with a dual role for Lgals13: first in low levels acting as a priming insult promoting endothelial activation and angiogenic imbalance, and increasing later in the third trimester as a natural rescue response promoting maternal vasodilation to lower blood pressure (169). In the context of gestational diabetes mellitus (GDM), increased Lgals13 serum levels during the early second trimester and lower expression in trophoblast cells of the term placenta have been reported (170, 171). Dysregulation of *Lgals13* was suggested to contribute to an imbalance in inflammatory processes in the placenta during pregnancy and therefore possibly lead to GDM.

Interestingly, while Lgals13 has hemagglutination activity when tested with chicken erythrocytes, a recent report suggested that contrary to what was observed for other galectins, Lgals13 may not bind carbohydrates (172). Prior studies, however, had reported that not only the binding of Lgals13 to erythrocytes or T cells is carbohydrate-dependent (50, 173), but also that N-acetyllactosamine is the preferred disaccharide ligand for Lgals13 (50, 159). This inconsistency in the results from the aforementioned laboratories may reside in that Su et al. (172) had tested lactose as an inhibitor for Lgals13, as well as other carbohydrates, such as xylose and arabinose, that are unrelated to the structures recognized by most galectins. Nevertheless, the identification of natural ligand(s) for Lgals13 at the cell surface and extracellular matrix will be of great importance to better understand its role(s) during pregnancy (165).

GALECTIN-GLYCAN INTERACTIONS AS REGULATORS OF THE FETAL-MATERNAL DIALOGUE

Glycosylation is the most common and structurally diverse type of post-translational modification, affecting proteins, lipids and the extracellular matrix. Glycans play fundamental roles in most biological processes, thus it is not surprising that glycans are profusely expressed in the mammalian uterus (174). During implantation, the uterine epithelium and the outer trophoblast cell layer of the implanting embryo interact in a glyco-specific manner, such that perturbations of the system generally result in failure of implantation or poor placentation and compromised pregnancy outcomes. Glycans are essential functional groups that facilitate and influence the reproduction process. The synthesis of glycans relies on specific modification enzymes (glycosyltransferases and glycosidases) (Figure 2), and the glycode expressed in a particular tissue

is highly dependent on the cell type and its developmental, nutritional, and pathological state. The glycans within the glycome can have multiple functions during pregnancy. For example, N-linked glycans (attached to the nitrogen of an asparagine side-chain) play an important role in trophoblast cell invasion in early pregnancy (175, 176) and maternal-fetal tolerance (177, 178). O-Linked glycans (attached to the hydroxyl oxygen of serine, threonine, tyrosine, hydroxylysine or hydroxyproline side-chains) can influence recognition events during fertilization (e.g., sperm-egg interactions) (179). As a detailed discussion about the role of glycosylation—in pregnancy outcome is beyond the scope of this review, we will focus on modifications that affect binding and function of members of the galectin family during gestation.

Extracellularly galectins act by cross-linking N- and O-glycans on the surface glycoproteins of maternal immune cells, trophoblasts and endothelial cells at the fetal-maternal interface. As glycosylation often represent highly regulated post-translational modifications related to the physiological cellular status, alterations in glycan composition can fundamentally impact galectin activity (180–182). Given the prominent expression of galectins (e.g., Lgals1 and Lgals3) at the fetal-maternal interface, studies designed to examine the relevance of cell surface glycans on maternal/ placental compartments are of key importance. In a physiological context, enhanced expression of N-acetylglucosaminyl transferase V [GnTV, encoded by the *Mgat5* gene (Figure 2)] was found in placentas from the first trimester compared with those from full-term pregnancies (175). GnTV generates β 1-6-N-acetylglucosamine branches in complex N-glycans which are recognized by Lgals1. LacNAc motives are a glycan signature of EVT (91, 183) as their presence was detected not only on their surface but also on their secretion product HLA-G (91, 184). Since Lgals1 promotes trophoblast invasion and EVT differentiation during early pregnancy (90), it is possible that the increased activity of GnTV results in enhanced Lgals1 signaling (176); particularly, by promoting the interaction of Lgals1 with β 1 integrin at the trophoblast cell membrane (94, 176, 185–190) (Figure 3). Furthermore, the presence of (β -6) branches and the expression of the glycosyltransferase GnTV involved in the generation of these glycan structures were reduced in villous tissues from early spontaneous miscarriages in comparison with healthy pregnancy villous tissues (191). Thus, differences in the glycan composition of trophoblast related-proteins at the same gestational age could be important disease biomarkers that should be further explored with newly available mass spectroscopy techniques. Indeed, the expression of GnTV was reported to be elevated in PE placentas compared to normal placentas (192). We have shown that *Lgals1* expression is increased in late onset PE and could represent a compensatory mechanism of the trophoblast to overcome the severe inflammation microenvironment that characterizes PE disease (74) (Figure 3). This is an interesting link to the metabolic status of trophoblast cells, which is mediated by the intracellular levels of GnTV that affect quality and branching of complex N-glycans and therefore regulate galectin binding.

During pregnancy the STB layer of the placenta releases extracellular vesicles (STBEV) containing a complex cargo of RNAs, proteins, lipids, and also glycans into the maternal

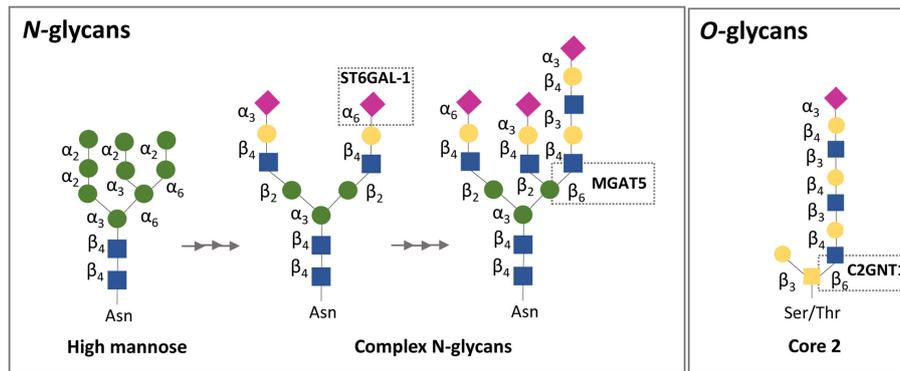


FIGURE 2 | Simplified schematic representation of *N*- and *O*-glycan biosynthesis focusing on galectin-1 binding affinity. *N*-glycans are attached to asparagine (Asn) residues, whereas *O*-glycans are attached to either serine (Ser) or threonine (Thr) residues. Gal-1 recognizes galactose on complex *N*-glycans and sialylation on the terminal galactose in the α 2,6-linkage, but not in the α 2,3-linkage, prevents the binding of gal-1. Regarding *O*-glycans, gal-1 binds to the *N*-acetylglucosamine (LacNAc) motif in core 2 *O*-glycans. ST6GAL-1, β -galactoside α 2,6-sialyltransferase 1; MGAT5, α 1,6-mannosylglycoprotein 6 β -*N*-acetylglucosaminyltransferase; C2GnT, core 2 β 1,6 *N*-acetylglucosaminyltransferase.

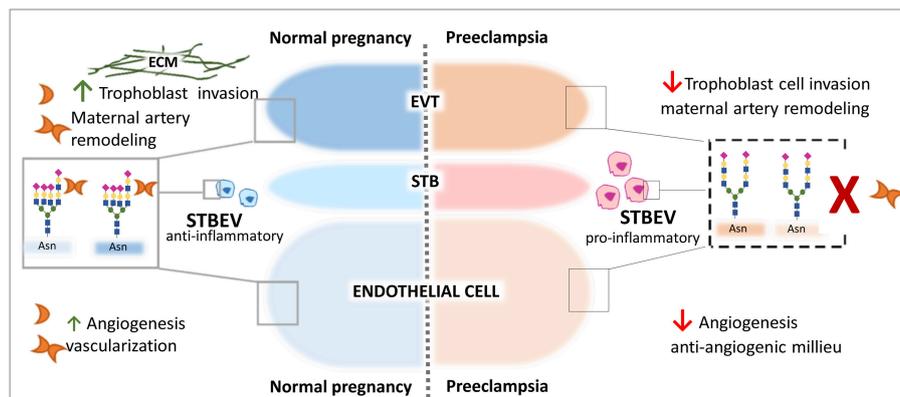


FIGURE 3 | Galectin-1-Glycan axis in the control of pregnancy protective programs. Galectin-1 regulates key process during the course of normal gestation including trophoblast invasion, maternal immune regulation, and angiogenesis. Relevant examples are illustrated. During Preeclampsia an aberrant α 2-6 sialylation decorates α 5 β 1 integrin on the cell surface of EVT trophoblast, cell surface of STBEV released from the STB trophoblast and on endothelial cells. The high expression of α 2-6 sialylated *N*-glycans impairs gal-1-mediated trophoblast ETV cell migration process interfering with the binding to the ECM and subsequently invasion. High α 2-6 sialylation on STBEV and impaired gal-1 binding might contribute to the pro-inflammatory milieu in maternal circulation and endothelial dysfunction. On vascular endothelial cells, the aberrant α 2-6 sialylation may disrupt gal-1-mediated angiogenesis and early vascularization promoting the anti-angiogenesis status typical of the syndrome.

circulation potentially to induce maternal immune adaption. Under pathological conditions such as preeclampsia, however, STBEV exhibit a differential glycan composition compared to uneventful pregnancies. In particular, STBEV derived from PE placentas depict an increased content α 2-6-linked sialic acid (193). The presence of α 2-6-linked sialic acid on cell surface glycoproteins—is mainly determined—by the activity of the sialyltransferase gene *ST6GAL1* and results in blocking of Lgals1 signaling (194, 195). The selective glycosyltransferase expression (e.g., ST6Gal-1) on trophoblast cells may be an early pathological mechanism of masking Lgals1 activity in modulating the maternal immune response to the developing embryo. Moreover, an increased α 2-6 sialylation was observed on the STB layer and also in placenta vessels derived from

pregnancies complicated with hypertensive disorders including superimposed PE, PE, and PE + HELLP (196). This is important since high α 2-6 sialylation on endothelial cells can reduce Lgals1 mediated angiogenesis (195), which is in line with our *in vivo* experiment showing that blocking Lgals1 mediated angiogenesis with anginex during early gestation in mice induced spontaneously PE development (74) (Figure 3). Moreover, the inhibition of Lgals1 binding by sialylation at the position 6 of galactose has been suggested to make Th1 cells resistant to apoptosis (197) and might contribute to uncontrolled maternal inflammation during preeclampsia. Thus, analysis of the glycosylation signature of trophoblast and placental vessels constitute a valuable approach to unravel the importance of galectin signaling through VEGFR2 during gestation.

CONCLUSIONS AND FUTURE DIRECTIONS

There is ample evidence showing that galectins are expressed widely at the fetomaternal interface. Their expression is regulated during pregnancy and galectins are highly specific to certain trophoblast and maternal cell types. Multiple galectin functions have been described in the orchestration of healthy pregnancy, which include maternal immune adaptation, placental development, and angiogenesis. Studies on the association of pregnancy pathologies with dysregulated galectin expression are still at an early stage, with most of our knowledge on the biological role of galectins in pregnancy being inferred from *in vitro* models and clinical correlations. However, sufficient evidence is already available to suggest galectins, especially Lgals1 and Lgals13, are promising candidates for further investigation aimed at understanding the pathogenesis of pregnancy complications including life-threatening pregnancy-related diseases such as PE. Because galectins are unique proteins with ability to recognize and decode a complex array of glycan motifs, future research could include: (1) a systemic study of the trophoblast cell-type glycome and galectin expression at the maternal-fetal interface in health and disease to determine whether glycomodifications on trophoblast cells that prevent galectin binding are responsible for the development of some pregnancy disorders and what is the galectin distribution in the maternal and placental compartments in health and disease; (2) a comprehensive analysis of the role of galectins in maternal circulation during pregnancy to establish whether galectins act at distance and if the presence of galectins in maternal circulation is

a consequence of leakage from placenta tissue; (3) a deep analysis of galectin-glycan interactions either at the maternal or placental compartments with the goal to reveal the critical contribution of the physiological and pathophysiological galectin functions during gestation. In the years ahead, the development of novel *in vivo* strategies to test hypotheses related to the biology of galectin-glycan interactions during pregnancy represents a worthwhile pursuit, which will greatly advance reproductive medicine.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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