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Galectins in angiogenesis: consequences for gestation

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ABSTRACT

Members of the galectin family have been shown to exert several roles in the context of reproduction. They contribute to placentation, maternal immune regulation and facilitate angiogenesis encompassing decidualisation and placenta formation during pregnancy. In the context of neo-vascularisation, galectins have been shown to augment signalling pathways that lead to endothelial cell activation, cell proliferation, migration and tube formation *in vitro* in addition to angiogenesis *in vivo*. Angiogenesis during gestation ensures not only proper foetal growth and development, but also maternal health. Consequently, restriction of placental blood flow has major consequences for both foetus and mother, leading to pregnancy diseases. In this review we summarise both the established and the emerging roles of galectin in angiogenesis and discuss the possible implications during healthy and pathological gestation.

1. Introduction

During gestation, proper placental function is critically important for the normal development of the embryo and foetus. As the placenta develops, angiogenesis of maternal vessels and remodelling of the spiral arteries ensure a constant supply of nutrients and oxygen. Angiogenesis is an essential process that ensures not only proper foetal growth and development, but also maternal health during gestation (Reynolds and Redmer, 2001; Chen and Zheng, 2013). In this review we provide an overview of galectin involvement in placental angiogenesis during gestation, and discuss the consequences of dysregulated galectin expression in pregnancy disorders such as preeclampsia.

2. Regulation of angiogenesis

Angiogenesis is defined as the formation of new capillaries from pre-existing vessels. In the placenta, capillary extension occurs *via* endothelial sprouting towards an angiogenic stimulus (branching), or *via* intussusceptive angiogenesis (splitting), a process in which transvascular tissue pillars form and expand to create a branched vessel (De Spiegelaere et al., 2012). Before 24 weeks' gestation in humans, placental blood vessels are formed mainly by the process of branching and splitting. After 24 weeks, when demands for increased blood flow to the foetus are at their highest, placental angiogenesis involves mainly the formation of capillary loops through elongation (Kaufmann, 1985). The result is a highly vascularised organ with an estimated capillary length of 550 km in the late-gestation human placenta (Burton and Jauniaux, 1995). At the cellular level, the progression of angiogenesis involves endothelial cell (EC) activation and proliferation, migration and alignment, tube formation and anastomosis (cross-connection between adjacent vessels) (Chung and Ferrara, 2011).

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During the angiogenesis process, activation of endothelial cells leads to cell surface endoglin (Eng) expression, a pleiotropic factor regulating cell proliferation, differentiation, migration and adhesion. Membrane-bound Eng is an accessory co-receptor that interacts with both transforming growth factor beta (TGF-β) and the TGF-β receptor type II to initiate pro-angiogenic functions. The membrane-bound form can also be cleaved from the membrane, resulting in anti-angiogenic soluble Eng (sEng) (Gregory et al., 2014). The placenta is a rich source of both pro- and anti-angiogenic factors that regulate blood vessel growth. During placentation, angiogenesis is spatiotemporally regulated by vascular endothelial growth factors (VEGF), TGF-β, fibroblast growth factors and angiopoietins (Kim et al., 2013). For the sake of brevity, this review will focus on the interaction of galectins with the VEGF family of pro-angiogenic growth factors.

In 1983, Senger et al. identified VEGF as a causative agent of vascular permeability in tumours (Senger et al., 1983). Over 30 years later, this protein has been recognised as one of the most important regulators of vasculogenesis and angiogenesis. At present, the VEGF family consists of several members; the original VEGF, which has been renamed VEGFA, VEGFB–F and placental growth factor (PlGF). Of the molecules involved in placental angiogenesis, VEGFA and PlGF are of major importance in all gestational stages (Nieminen et al., 2014). Expressed in the human endometrium, decidua (Torry and Torry, 1997) and trophoblast (Shore et al., 1997; Reynolds and Redmer, 2001), and increasing in expression with gestational age, VEGFA stimulates vascular EC activation and migration, in addition to vascular permeability (De Falco, 2014). The importance of this molecule is demonstrated by mouse models, where disruption of the VEGFA gene is embryonically lethal because of a failure of proper blood vessel formation during embryonic vasculogenesis and angiogenesis (Carmeliet, 2000). The VEGFA gene undergoes alternative splicing to produce up to nine isoforms, distinguished by their ability to bind to heparan sulphate proteoglycans in the extracellular matrix. This results in differing spatiotemporal expression and activity for each VEGF isoform, and suggests that VEGFA function is strongly influenced by the tissue microenvironment (Vempati et al., 2011; Arcondeguy et al., 2013). Named after the number of amino acids in the mature protein, the $VEGFA_{121}$, $VEGFA_{165}$ and $VEGFA_{189}$ isoforms are the most important for placental angiogenesis (Arcondeguy et al., 2013).

Placental growth factor (PlGF) is an additional VEGF family member that undergoes alternative splicing to produce four isoforms. PlGF participates in the formation of the placental vascular network and the development of the villous tree (Chen and Zheng, 2013). PlGF stimulates the proliferation of fibroblasts and smooth muscle cells (Yonekura et al., 1999; Bellik et al., 2005), recruits myeloid progenitors to growing sprouts (Pipp et al., 2003; Scholz et al., 2003) and attracts pro-angiogenic macrophages to angiogenesis sites (Selvaraj et al., 2003). Although PlGF knockout mice are viable, foetal and placental weights in these animals are reduced (Lijnen et al., 2006); providing further evidence that PlGF is an important protein involved in healthy placental growth and development.

The VEGF family members activate angiogenic mechanisms in the placenta through the transmembrane tyrosine kinase binding receptors VEGFR1 (also known as Flt-1) (Shalaby et al., 1995) and VEGFR2 (also known as KDR or Flk-1) (Fong et al., 1995), in conjunction with a neuropilin (NRP) co-receptor (Tsoi et al., 2002). Although the pro-angiogenic cascade is initiated by VEGF binding to VEGFR, NRP-1 and -2 are essential for strong and sustained receptor activity (Soker et al., 2002; Becker et al., 2005). Similar to VEGFR knockouts, NRP-1 null mice die at embryonic day 10.5 because of defective vasculature formation (Jones et al., 2008). In addition to their interaction with transmembrane receptors, VEGF and PlGF can also be bound by soluble VEGFR (sVEGFR1, also called, s-Flt1). s-VEGFR1 acts in an anti-angiogenic manner, sequestering VEGF and PlGF and preventing the initiation of angiogenic signalling cascades (Krüssel et al., 2003).

Angiogenesis is a finely tuned process and healthy placentation requires a balance between pro-angiogenic stimulation of blood vessel growth, and anti-angiogenic prevention of vessel overgrowth. Disturbance of this balance through over- or under-expression of particular angiogenic molecules leads to poor placental growth and perfusion, which is ultimately detrimental to pregnancy.

3. Dysregulation of placental angiogenesis and pregnancy disorders

A healthy placenta has long been acknowledged to be a keystone of foetal development, and nearly all pregnancy complications have been linked to improper development of the placental vasculature (Chen and Zheng, 2013). Restriction of placental blood flow has major consequences for both foetus and mother during gestation. Increased vascular resistance and reduced uterine blood flow are associated with intrauterine growth restriction, and are predictors of high-risk pregnancies (Reynolds and Redmer, 2001). On the maternal side, the demand for increased blood flow in an improperly formed placenta has dangerous consequences for maternal health, leading to pregnancy diseases such as preeclampsia.

4. Preeclampsia

Preeclampsia (PE) is defined as gestational hypertension and proteinuria developing in the second half of pregnancy, with early onset PE (the most severe form) developing at <34 weeks' gestation. With a prevalence of 3–5%, PE remains a significant public health problem; it is the leading cause of maternal and neonatal mortality worldwide, especially in developing nations (Doridot et al., 2013; Al-Jameil et al., 2014). PE has major consequences for both mother and child, during pregnancy and later in life. Maternal hypertension during gestation is a common feature of PE due to increased peripheral vascular resistance. This hypertensive state can proceed to permanent vascular and metabolic damage, which elevates the long-term risk of cardiovascular disease (Irgens et al., 2001; Berends et al., 2008; Sibai, 2008) and diabetes (Lykke et al., 2009) for the mother. Considering foetal development, in some cases, PE is also a risk factor for intrauterine growth restriction owing

to the decreased placental perfusion and lack of appropriate blood supply (Sibai, 2008).;

Pathological examination of placentas from women with severe PE reveals infarction (necrosis), thrombosis, vascular lesions and chronic inflammation. Abnormal placentation subsequently results in the liberation of placental debris and release of anti-angiogenic factors into the maternal circulation (Doridot et al., 2013; Al-Jameil et al., 2014). Of the molecules released by an improperly perfused placenta, soluble endoglin (sEng) (Venkatesha et al., 2006) and sVEGFR1 (sFlt1) (Kupferminc et al., 1997) are major contributors to endothelial dysfunction. Demonstrating this experimentally, administration of sVEGFR1 to pregnant rats leads to PE-like symptoms including hypertension, proteinuria and glomerular endotheliosis (kidney lesions) (Maynard et al., 2003). Clinically, preeclampsia is associated with increased maternal serum concentrations of sVEGFR1 (s-Flt1) and decreased concentrations of PlGF (Torry and Torry, 1997; Levine et al., 2004). Additionally, overexpression of sVEGFR1 and sEng is also correlated with preeclampsia severity (Koga et al., 2003; Maynard et al., 2003; Venkatesha et al., 2006).

5. Galectins: multifunctional regulators at the foetal–maternal interface

The galectin (gal) family, defined by a canonical carbohydrate recognition domain (CRD) of approximately 130 amino acids with specificity for β-galactosides, represents the most widely expressed class of lectins in all organisms (Barondes et al., 1994). Nineteen mammalian galectins have been described to date, of which 13 are expressed in human tissues (Cooper, 2002). Structurally, the galectin family is further classified into three groups according to the number and arrangement of their CRDs: prototype, tandem repeat and chimaera-type galectins (Barondes et al., 1994). Thus, galectins containing a single CRD (*i.e.* gal-1, -2, -5, -7, -10, -13, -14, -15, -16, -17, -19), and usually found as homodimeric forms, are defined as a 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 on them multivalent binding activities. Finally, chimaera-type galectins (of which the only member known to date is gal-3) are characterised by a C-terminal CRD and an N-terminal non-lectin domain of proline- and glycine-rich short tandem repeats involved in multimerisation and proteolytical regulation (Barondes et al., 1994; Brewer et al., 2002).

Galectins display a wide array of biological functions in both the intra- and extracellular milieus. Intracellularly, they engage in protein–protein interactions modulating various processes including cell growth, differentiation, survival and migration (Liu et al., 2002). Alternatively, galectins can be exported from cells by a non-classical mechanism (Nickel, 2005) and regulate different responses mediated by their lectin activity (Brewer et al., 2002). Thus, 'secreted' galectins can function extracellularly to modulate cell adhesion and apoptosis or as cytokine-like molecules in the regulation of innate and adaptive immunity (Hernandez and Baum, 2002; Rabinovich et al., 2007). This functional heterogeneity has made galectins an appealing subject in reproductive medicine, especially after the recognition of their pivotal role in immune–endocrine interactions during the establishment and maintenance of pregnancy (Blois et al., 2007; Than et al., 2009; Tirado-Gonzalez et al., 2013). Studies profiling galectin expression in reproductive tissues have multiplied in the past few years, highlighting the importance of a delicate interplay between maternally and fetally derived sources for successful reproductive outcomes and providing important insights into their role in pregnancy (Fig. 1).

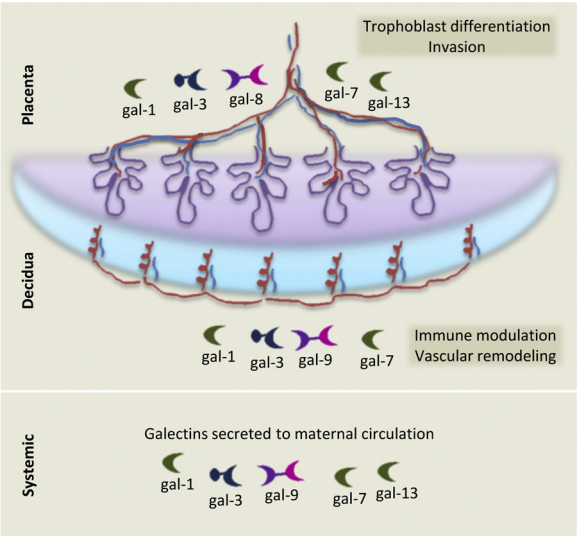

Fig. 1. Sources of galectin expression during human pregnancy. During gestation, galectins are expressed in both the maternal and foetal compartments where they participate in multiple processes important for sustaining foetal growth. Maternally derived galectins (*i.e.* those expressed in decidual tissue) engage in cell–cell and cell–matrix interactions to facilitate embryo implantation and trophoblast invasion during placentation, as well as to modulate maternal immune cell function towards a tolerogenic profile. Numerous galectins are also differentially expressed in the placenta, where they appear to play significant roles in the differentiation, migration and invasion of trophoblast cells, and may participate in villous angiogenesis. While their maternal or foetal origin is still difficult to identify, galectins are also found in the maternal circulation and may serve as biomarkers for diverse pregnancy disorders, including preeclampsia and spontaneous abortion.

Among prototypic galectins, the best studied in the context of pregnancy is gal-1. This lectin is one of the most abundantly expressed galectins in female reproductive tissues, particularly in the endometrium/decidua where its expression fluctuates under the control of ovarian steroids (von Wolff et al., 2005). The spatiotemporal pattern of endometrial gal-1 expression, which is similar in mice and humans, indicates a possible role in blastocyst attachment and endometrial immune regulation during implantation (Choe et al., 1997; von Wolff et al., 2005). Indeed, the well-known immunomodulatory functions of this lectin appear to be critical for pregnancy maintenance, acting as a tolerogenic signal to favour the induction of IL-10 producing dendritic cells (DC) and regulatory T cells *in vivo* (Blois et al., 2007) in addition to promoting immune escape mechanisms of human placental trophoblasts *in vitro* (Tirado-Gonzalez et al., 2013). Besides

endometrial gal-1, foetal/placental expression of the lectin also plays a significant role in the developmental processes associated with pregnancy (Barrientos et al., 2014). In humans, the lectin is detected in the pre-implantation stages on the embryonic trophectoderm (Tirado-Gonzalez et al., 2013), later being differentially distributed in the villous and extravillous trophoblast cell lineages derived from this tissue. Placental gal-1 appears to function as a local modulator of both pathways of trophoblast cell differentiation, as the lectin has been shown to stimulate cell fusion and syncytin expression by villous CTB *in vitro* (Fischer et al., 2010) in addition to promoting adhesion and invasion of HTR-8/SVneo cells and primary extravillous trophoblasts (EVT) cultured in Matrigel (Kolundzic et al., 2011). Besides gal-1, regulatory functions have been attributed to two other prototypic galectins during human pregnancy. Gal-13 is largely restricted to human placenta, where it was originally identified as placental protein 13 (PP13) (Than et al., 1999). This lectin localises to the syncytiotrophoblast and occasionally to multinucleated luminal trophoblasts within converted spiral arterioles, suggesting a role in trophoblast invasion and vascular remodelling during placentation (Kliman et al., 2012). Gal-13 has also been shown to promote apoptosis of activated T cells and macrophages (Than et al., 2009) and may thus participate in the modulation of maternal immune responses during pregnancy. Indeed, gal-13 is often detected as extracellular aggregates associated with T-cell-, neutrophil- and macrophage-containing decidual foci of necrosis (Kliman et al., 2012), suggesting that the secretion of the lectin might be a mechanism to attract and activate maternal immune cells facilitating trophoblast invasion and arterial remodelling. More recently, gal-7 was identified as the third prototype member expressed at the foetal–maternal interface, localising mainly to syncytiotrophoblast and the EVT of first-trimester placentas and also to placental endothelial cells at term (Menkhorst et al., 2014a). While the functional significance of placental gal-7 is still largely elusive, endometrial expression of the lectin has been suggested to facilitate adhesion of the embryo to the endometrium during implantation, a notion supported by the selective localisation of the protein to the luminal and glandular epithelia and by its ability to stimulate endometrial epithelial trophoblast adhesion in cell-line and primary cell assays *in vitro* (Menkhorst et al., 2014b). Interestingly, several lines of evidence link the dysregulated serum levels of these three prototype galectins with pregnancy complications such as spontaneous abortion and preeclampsia (Freitag et al., 2013; Huppertz et al., 2013; Tirado-Gonzalez et al., 2013; Menkhorst et al., 2014a), indicating their potential application as early diagnosis biomarkers (Fig. 1).

The only chimaera-type member identified so far, gal-3, is also abundantly expressed at the foetal–maternal interface, with a distribution pattern highly coincident with that of gal-1 (Vicovac et al., 1998; von Wolff et al., 2005). Indeed, the interplay between the two lectins may be important for maternal immune homeostasis during early pregnancy, as gal-3 functions mainly as a pro-inflammatory mediator promoting T cell proliferation and activation as well as cytokine secretion from innate immune cell subsets (Iglesias et al., 1998; Chen et al., 2005; Alves et al., 2010). While the profile of gal-3 expression at the foetal–maternal interface has been well characterised in several species, its physiological relevance during pregnancy is still largely elusive. In mice, gal-3 selectively localises to the uterine luminal epithelium and primary decidual zone during early pregnancy, later being predominantly expressed in the placenta (Phillips et al., 1996). This expression pattern highlights the potential role of the lectin in the embryo–maternal communication during the implantation process, as suggested by the decreased implantation rates observed upon tissue-specific knockdown of *Lgals3* in the mouse uterus (Yang et al., 2012). The human lectin shows a similar spatiotemporal distribution at the foetal–maternal interface, being up-regulated in the late secretory phase endometrium and the decidua of early pregnancy and switching to placental villi and the EVT as gestation progresses (Maquoi et al., 1997; von Wolff et al., 2005). Thus, a possibility that awaits further investigation is the involvement of this lectin in the modulation of trophoblast differentiation during placentation, particularly in view of recent studies showing a significant up-regulation of gal-3 protein upon hypoxia-induced syncytialisation in the BeWo cell line (Hu et al., 2007). Additionally, several studies have attributed pro-angiogenic properties to this lectin (Nangia-Makker et al., 2000b; Fukushi et al., 2004; Wan et al., 2011; Machado et al., 2014), which are anticipated to be significant for vascular responses associated with pregnancy and are discussed in detail in the following sections.

As for tandem repeat galectins, the only members identified to date at the foetal–maternal interface include gal-8, gal-9 and gal-4, although the latter has only been described in rat placenta and scant information on its physiological role is available (Arikawa et al., 2012). Expression of gal-8 was also recently reported in the context of pregnancy (Kolundzic et al., 2011b); thus, its functional consequences remain largely speculative based on observations in other settings. Since gal-8 expression is selectively localised to the placental EVT columns, it may play a role as a physiological modulator of ECM remodelling, cell adhesion and migration during the invasive process. Indeed, gal-8 shows the ability to form molecular complexes with integrins through carbohydrate–protein interactions acting as a positive or negative modulator of cellular adhesion (Zick et al., 2004). The gal-8–integrin interaction may also contribute to decidual immune trafficking and homeostasis, as demonstrated by the ability of gal-8 to induce leucocyte adhesion to endothelial cells and ECM components (Nishi et al., 2003; Yamamoto et al., 2008). A role has also been attributed to the lectin in the modulation of T cell function and angiogenesis (Cattaneo et al., 2011), which make it an attractive candidate for performing regulatory functions in the context of pregnancy (Delgado et al., 2011). With regard to gal-9, this tandem repeat member is considered mainly an immunomodulatory galectin owing to its influence on T cell survival and activation. Gal-9-mediated immune regulation depends largely upon interaction with its cell surface receptor TIM-3, and includes both stimulatory effects on macrophage and DC activation and immune silencing by enhancing apoptosis of Th1 lymphocytes (Zhu et al.,

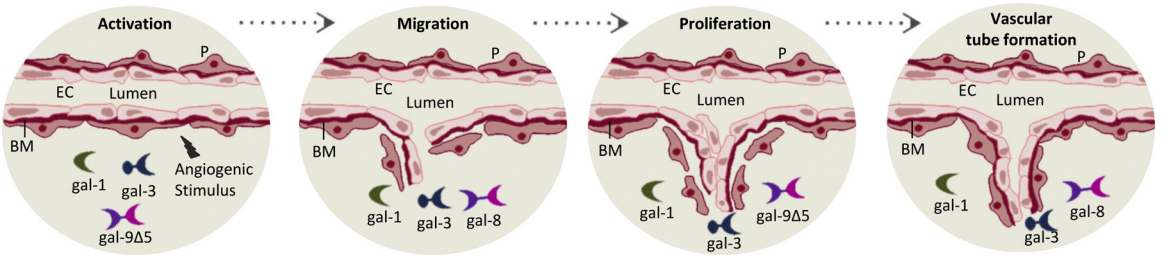

Fig. 2. Key stages in the process of angiogenesis influenced by galectins. The diagram summarises the steps in which several galectin members are involved in the formation of new blood vessels. Steps include endothelial cell activation, endothelial cell migration, proliferation, and vascular tube formation. Both gal-1 and gal-3 stimulate multiple endothelial functions during angiogenesis, whereas gal-8 and gal-9 Δ5 influence specific steps of the angiogenesis cascade (gal-8, migration and vascular tube formation; gal-9 Δ5, activation and proliferation of endothelial cells). EC, endothelial cells; BM, basement membrane; P, pericytes; gal-1, galectin-1; gal-3, galectin-3; gal-8, galectin-8; gal-9Δ5, splice variant galectin-9 lacking exon 5.

2011). Additionally, gal-9 exerts anti-inflammatory effects through TIM-3-independent mechanisms, promoting the generation of Foxp3$^+$ regulatory T cells and suppressing Th17 cell activity (Oomizu et al., 2012). In humans, endometrial gal-9 expression is found mainly on epithelial cells and markedly up-regulated in decidua (Popovici et al., 2005), implying a possible role in local immune suppression. Indeed, the expression of at least six gal-9 isoforms has been demonstrated in human decidua, further showing that *Lgals9 Δ5* displays the ability to suppress IFN-γ production by uterine NK cells (Heusschen et al., 2013). These studies further demonstrated that abortion-prone mouse pregnancies are associated with an abnormal pattern of decidual gal-9 isoform expression and significantly decreased levels of the *Lgals9 Δ5/10* splice variant in spontaneous abortion patients (Heusschen et al., 2013). While placental expression of gal-9 has also been reported in several species (Thijssen et al., 2008; Froehlich et al., 2012), its physiological relevance awaits further investigation.

6. Galectins involved in angiogenesis

Research over the past decade has shown that the process of angiogenesis could also be mediated by carbohydrate recognition (Nangia-Makker et al., 2000a), and identified the critical role of galectin–glycan interactions during this process. Galectins have been shown to be involved in several steps of the angiogenesis process (Fig. 2). For instance, the expression and distribution of endothelial galectins are altered on EC cell activation, designating them as early markers of this process (Thijssen et al., 2008). Gal-1 expression is increased upon EC activation *in vitro* and although a proportion of galectin is expressed intracellularly, gal-1, -8 and -9 are translocated to the outer surface of EC during activation. In addition, angiostimulatory activities have been attributed to several galectins *in vitro* and *in vivo*. These include the ability of gal-1 to bind the NRP-1 on human umbilical vein endothelial cells (HUVEC), which functions as a co-receptor of VEGFR2 (Fig. 2). The activation of VEGFR2 *via* NRP-1 and modulation of the JNK signalling pathways increases proliferation and adhesion of EC and thereby enhances cell migration (Fig. 3) (Hsieh et al., 2008).

It has been shown that exogenous gal-3 promotes endothelial cell migration and capillary tube formation (Nangia-Makker et al., 2000b). Recently, Markowska and co-workers (2010) demonstrated that the gal-3 CRD binds to GnTV modified N-glycans on αvβ3 integrin. Gal-3 cross-links and clusters the integrin, then activates FAK, mediating signalling pathways that modulate events such as EC cell migration (Fig. 3). Furthermore, experiments *in vivo* and *in vitro* have also determined that gal-3 interacts with N-glycans of VEGFR2 in an Mgat-5-dependent manner, increasing the density of VEGFR2 on the plasma membrane, which is now accessible to the endogenous VEGFA and thus enhances the intracellular signalling involved in EC proliferation, migration and survival (Fig. 3) (Markowska et al., 2011). The combined effect of exogenous gal-1 and gal-3 on angiogenesis-related events has also

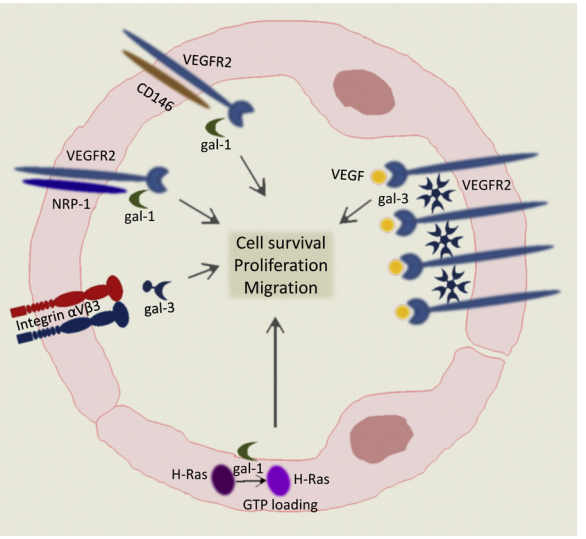

Fig. 3. Receptors involved in endothelial cell function by galectins. Pro-angiogenesis signalling could be facilitated by the interaction between gal-1 and CD146. In addition, gal-1 enhances VEGFR2 signalling by interacting with NRP-1. Through the interaction with the integrin αVβ3, gal-3 facilitates FAK signalling assisting membrane anchorage of H-Ras-GTP. Finally, gal-3 activates with N-glycans of VEGFR2 in an Mgat-5-dependent manner, increasing the density of VEGFR2 on the plasma membrane, which is now accessible to the endogenous VEGFA, and thus enhancing the intracellular signalling cascades in EC proliferation, migration and survival. Endothelial cells are shown in pink. *Abbreviations*: gal-1, galectin-1; gal-3, galectin-3; gal-8, galectin-8; VEGFR2, vascular endothelial growth factor receptor 2; NRP-1, neuropilin-1.

been investigated recently (D'Haene et al., 2013). Using two different EC cell lines, D'Haene and co-workers determined that both galectins mediate VEGF activation by increasing the density of VEGFR1 and VEGFR2 on the cell surface, making them accessible to low levels of endogenous VEGF. Signalling pathways downstream of VEGF receptors activated following the addition of galectins involved the MAP kinase pathway (ERK) and Hsp27. While activation of ERK may be involved in the endothelial cell proliferative effect induced by galectins, Hsp27 signalling is associated with endothelial cell migration and tube formation (D'Haene et al., 2013).

Gal-8 also participates in angiogenesis regulation. Indeed, exogenous and endogenous gal-8 promotes EC migration and tubulogenesis *in vitro* and modulates angiogenesis *in vivo via* interaction with CD166 (Delgado et al., 2011). Gal-8 also binds a variety of integrins such as $\alpha 3\beta 1$ and $\alpha 6\beta 1$ that are expressed on human vascular EC. This allows the regulation of cell–matrix interactions that influence cell adhesion and survival (Hadari et al., 2000). Besides gal-8, involvement in endothelial cell biology was recently attributed to a second tandem-repeat galectin, gal-9. Heusschen and co-workers showed that gal-9 protein levels increased on the tumour endothelial cells compared with the normal endothelium, gal-9Δ5 being the most abundantly expressed splice variant in quiescent endothelial cells (Heusschen et al., 2014). However, when endothelial cells are activated *in vitro* the RNA levels of gal-9 are down-regulated, mainly caused by a decreased expression of the gal-9Δ5 splice variant. In addition, the authors showed that the contribution of gal-9Δ5 to endothelial cell function depended on the concentration and context in which the protein was presented to the cell. Thus, endogenous gal-9Δ5 induced a modest increase in endothelial cell proliferation and had no effect on migration. Exposure of exogenous gal-9Δ5 does not provoke proliferation of endothelial cells, however, and does not affect sprout formation; applying the protein locally resulted in increased sprouting, suggesting that gal-9Δ5 might act as a chemoattractant for HUVEC cells (Heusschen et al., 2014). Overall, the function of galectins in endothelial cell biology is diverse because of their localisation in different cell compartments (*i.e.* the nucleus, cytoplasm and the cell membrane), transcriptional post-translational modification and mRNA splicing. Consequently, further research in the field of galectins and endothelial cell biology will address individual and complementary roles of this family of lectins.

7. Regulation of the angiogenesis process associated with pregnancy by galectins

Pro-angiogenic functions of gal-1 have been well studied in several physiological conditions (Thijssen et al., 2007) and we have recently shown that gal-1 is also involved in angiogenic processes at the feto-maternal interface during pregnancy (Freitag et al., 2013). In a mouse model of reduced vascular expansion (Plaks et al., 2008), administration of exogenous gal-1 increased angiogenic factors such as plasminogen activator inhibitor-1, fibroblast growth factor-basic, angiogenin, plasminogen and tissue factor. It also increased the expression of proteins that are important for matrix remodelling (*e.g.* matrix metallopeptidases) in order to maintain normal vascular development. Gal-1 thereby rescued the implantation process and supported healthy placentation in these mice.

During gestation, gal-1 mediates its signals *via* the VEGF–VEGFR2 pathway (Fig. 3) (Hsieh et al., 2008; Douglas et al., 2009). VEGF binds VEGFR2 on endothelial cells, thereby enhancing angiogenic processes during implantation, decidualisation and placentation. Both factors are abundantly expressed in the murine and human female reproductive tract (Halder et al., 2000; Baston-Buest et al., 2011). Interestingly, the pregnancy-protective effect of gal-1 is abolished by DC101, a neutralising antibody that blocks VEGF–VEGFR2 signalling through interaction with NRP (Douglas et al., 2009; Freitag et al., 2013). Furthermore, the binding of gal-1 to NRP-1 promotes the interactions between VEGF and VEGFR2 and thus enhances the migration and adhesion of endothelial cells (Soker et al., 1998; Halder et al., 2000; Hsieh et al., 2008). During gestation, NRP-1 is expressed in the reproductive tissue of mice and humans suggesting the role of the gal-1/NRP-1/VEGF signalling pathway in angiogenic processes related to pregnancy (Halder et al., 2000; Baston-Buest et al., 2011).

In addition to these observations, recent studies have shown that the inhibition of gal-1-mediated angiogenesis with the synthetic peptide anginex results in a preeclampsia (PE)-like syndrome in mice and compromises human extravillous cytotrophoblast cell functions *in vitro* (Thijssen et al., 2006; Freitag et al., 2013). While the precise aetiology of PE remains largely elusive, some cases of the syndrome (*i.e.* the "placental type" of PE (Redman and Sargent, 2010; Staff et al., 2013)) appear to be linked to reduced invasion of foetal extravillous trophoblast cells and reduced remodelling of maternal uteroplacental spiral arteries as initial pathophysiological events. This leads to an unfavourable uteroplacental circulation, with enhanced oxidative, endoplasmic reticulum stress and release of placental anti-angiogenic factors such as sFlt-1 and sEng to the maternal circulation, causing endothelial dysfunction that manifests as hypertension and proteinuria (Maynard et al., 2003; Redman and Sargent, 2005; Venkatesha et al., 2006). Thus, our recent findings showing that *Lgals1*-deficient dams also exhibit PE-like features (Freitag et al., 2013) invite further exploration of the potential link between gal-1 pro-angiogenic effects at the foetal–maternal interface and the impaired endothelial function typical of this syndrome. Consistent with these findings, placental and peripheral gal-1 expression is down-regulated in patients diagnosed with early onset PE, which is mainly a consequence of placental dysfunction. In addition, we reported that gal-1 could serve as a valuable biomarker in anticipating the development of PE, highlighting its critical role in pregnancy complications associated with impaired angiogenesis.

Another galectin that may be involved in angiogenic processes during pregnancy is placental protein 13 (PP13), also known as gal-13. Gal-13 is specifically expressed in the syncytiotrophoblasts of the human placenta and serum levels increase over gestation, suggesting a specific role in pregnancy (Burger et al., 2004; Than et al., 2004, 2009;

Huppertz et al., 2008). Indeed, the secretion of gal-13 from syncytiotrophoblast into the intervillous space may lead to the remodelling of maternal spiral arteries by invasive trophoblasts (Kliman et al., 2012). In line with this, reduced gal-13 expression in syncytiotrophoblast is associated with PE (Than et al., 2008; Sekizawa et al., 2009). In PE patients, the serum levels are also reduced in the first trimester, but elevated gal-13 is found in the third trimester resulting from the increased placental shedding (Burger et al., 2004; Chafetz et al., 2007; Gonen et al., 2008; Romero et al., 2008; Than et al., 2008; Khalil et al., 2009). These results nominate gal-13 as a potential biomarker and drug for the early diagnosis and treatment of PE, respectively (Huppertz et al., 2013). Recently, the biological effect of gal-13 on the vasculature was analysed in rats (Gizurarson et al., 2013). A single injection of human gal-13 reduced the blood pressure *in vivo* and led to vasodilation in isolated arteries *in vitro*. Furthermore, a five-day treatment during late rat pregnancy increased the utero-placental perfusion. These results could explain the relationship among the reduced utero-placental blood flow, hypertension and dysregulated gal-13 levels observed in human PE patients.

8. Future research and conclusion

Angiogenic and vascular remodelling responses are critical for proper placental development and function and hence, successful pregnancy outcomes. Since the identification of pro-angiogenic functions exerted by galectin family members, studies analysing their role in physiological contexts such as pregnancy have multiplied, providing important insights into the mechanisms that modulate placental vascular development, as well as the consequences of dysregulated angiogenesis in terms of pregnancy disorders. In particular, the finding that expression of at least four galectins with pro-angiogenic properties appears to be altered in pregnancies complicated by preeclampsia establishes an important link between galectin-mediated vascular responses and the pathogenesis of this complex syndrome, inviting further exploration of their relationship with imbalanced angiogenic factor production, their possible involvement in maternal endothelial dysfunction, and their potential application as disease biomarkers. Future studies aimed at identifying the profile of expression of galectins and their molecular targets within the placental vascular network will provide important tools for the design of therapeutic interventions in reproductive medicine, with maternal and offspring health ultimately benefiting.

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