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REVIEW

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Extracellular matrix and pregnancy: functions and opportunities caught in the net

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Abstract

The extracellular matrix is a complex network of macromolecules that support the growth and homeostatic development of organisms. By conveying multiple signaling cascades, it impacts on several biological processes and influences the behaviour of numerous cell types. During the endometrial cycle and the key events necessary for a correct embryo implantation and placentation, this bioactive meshwork is substantially modified to favour endometrial receptivity and vascular adaptation, trophoblast cell migration, and immune activation as well. A correct extracellular remodeling is fundamental for the establishment of a physiological pregnancy; indeed, the occurrence of altered matrix modifications associates with gestational disorders such as preeclampsia. In the present review, we will critically evaluate the role of pivotal matrix constituents in regulating the key steps of embryo implantation and placentation, provide up-to-date information concerning their primary mechanisms of action and discuss on their potential as a novel source of biomarkers and therapeutic targets.

Keywords Pregnancy, Extracellular matrix, Endometrial receptivity, Decidualization, Placenta, Implantation, Tissue remodeling

Introduction

Pregnancy is a complex process that comprises separated and multistep events, including decidualization, implantation, and placentation [1]. For the maintainance of a healthy intrauterine environment capable of supporting a successful embryo implantation and a functional placentation, the efficient remodeling of tissue and vasculature within the uterus during the menstrual cycle and pregnancy is a basic requirement [2].

The massive tissue remodeling occurring along with decidualization and placentation is accompanied by dramatic alterations in composition, form, and functionality of the extracellular matrix (ECM), which is constantly deposited and degraded to support the evolving tissues [2]. The ECM is a net of fibrillar proteins, proteoglycans and glycoproteins that can interact with a variety of proteins, receptors and soluble factors, thus influencing a plethora of physiological and pathological processes [3–7].

During a healthy pregnancy, the ECM exerts both mechanical and biochemical functions, maintaining uterine structural integrity, facilitating embryo adhesion, and regulating trophoblast invasion into the endometrium (Fig. 1) [8, 9]. The ECM is readily degraded and built up again along with the processes of decidualization and placentation. This massive ECM remodeling is driven by the local cellular milieu and by secreted or cell-associated components in a framework of dynamic reciprocity [3].

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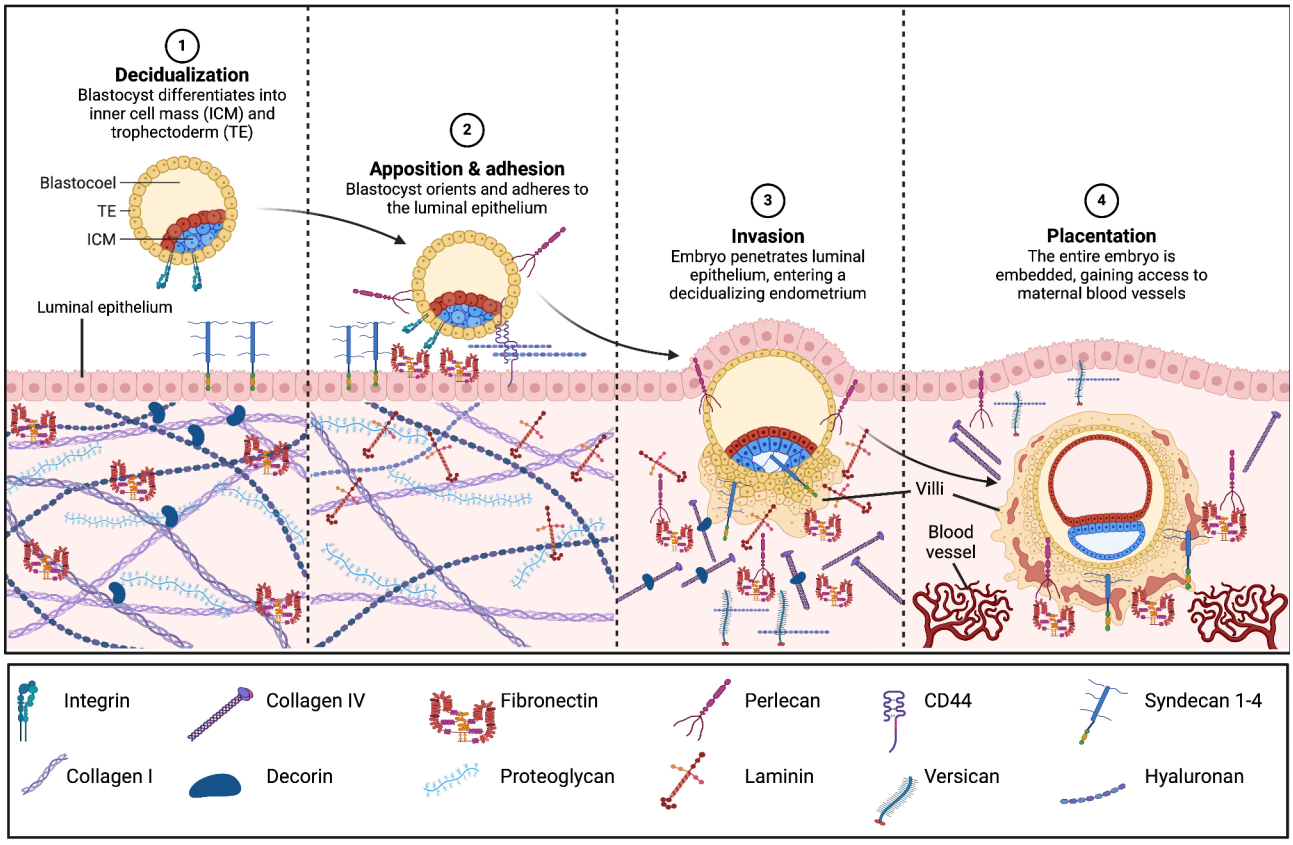

Fig. 1 A massive extracellular remodeling occurs during the menstrual cycle and the early phases of pregnancy, being instrumental for the establishment of a receptive decidua and guiding trophoblast cell differentiation and invasion. Created with Biorender

Through their receptors, primarily integrins, cells sense physical and biochemical characteristics of the microenvironment, including substrate stiffness, pressure, shear, and stretch, and convert these cues into intracellular signals that regulate cell structure and behaviour [3].

The proficient spatio-temporal regulation of ECM remodeling is crucial to support a physiological pregnancy and an altered expression of matrix molecules in the womb is associated with pathological conditions of reproduction and pregnancy, such as placenta accreta and preeclampsia [10–12].

Despite these observations, the study of ECM in pregnancy still represents an almost unexplored field and the data regarding the role of ECM molecules are sparse and disorganised.

The first evidence regarding the study of ECM molecules in the decidua and the placenta dates back to the 1980s and 1990s, as in the case of collagens and laminins [13–16]. Over time, more and more knowledge regarding the mechanisms by which they are remodeled and their functions in pregnancy has been gathered. Moreover, additional types of ECM components have been identified as relevant to these processes. Thus, in the present review, we aim to provide a comprehensive overview of the functions of key ECM components in the milestones that occur throughout gestation, and to relay state-of-the-art information concerning the mechanisms of matrix remodeling in physiological pregnancy and in reproductive and obstetric complications. Because of the intricate nature of the ECM molecules, which frequently engage in multifaceted mechanisms, a clear separation of their contributions to each distinct phase of pregnancy is not always feasible. However, as provided in the following paragraphs and Table 1, the review is organized to describe the functions exerted by ECM components along with the specific processes of decidualization, blastocyst adhesion, trophoblast invasion and placentation.

Decidualization: shaping the ECM to prepare the soil

The endometrium, the inner mucosal lining of the uterus, is a highly organized multicellular tissue that undergoes a cyclic dynamic remodeling to establish a microenvironment suitable for supporting a pregnancy. The endometrial cycle consists of two dominant phases: the proliferative phase, which is guided by oestradiol, follows menstruation and precedes ovulation, and the secretory phase, which occurs after ovulation [17]. During

Table 1 The table summarizes the main evidence regarding the involvement of ECM components in the various processes occurring in the early phases of pregnancy

ECM molecule	Decidua formation	Embryo apposition / adhesion	Trophoblast invasion	Vascular adaptation	Placental development	Immune modulation
Collagen I	Rapidly thickens and rearranges around the decidual cells and is necessary for a correct decidualization [29, 30, 37–39]		Functions as an adhesive substrate for trophoblasts, if excessively expressed suppresses the proliferation and invasion of trophoblasts through the inhibition of the ERK and WNT/β-catenin signaling [99–101]		Provides the villous structural scaffold [140]	Promotes Treg differentiation [52]
Collagen III	Rapidly thickens and rearranges around the decidual cells [29]		Promotes trophoblast migration [102]			
Collagen IV	Selectively up-regulated during decidualization [29, 30, 45]			Increases around the spiral arteries; participates in decidual vascular remodeling [45]	Expressed in the mesenchyme of placental villi, participates in glycocalyx formation [144]	
Collagen V	Rapidly thickens and rearranges around the decidual cells [29]					
Collagen XVIII	Widely expressed in the decidua during the first and third trimesters of pregnancy [44]		Degraded by MMPs releases endostatin, that inhibits trophoblasts invasion by binding to integrin α5β1 [105]			
Fibronectin	Supports the structural organization of the evolving ECM by interacting with other stromal proteins [50, 51]	Present on the luminal endometrial epithelium, interacts with α5β1 integrin expressed by the trophectoderm [60]	Binds to αIIbβ3 on trophoblasts [76, 77]; regulates trophoblast adhesion and migration into maternal tissue through the activation of Erk and Akt signaling pathways [107, 108, 110]	Promotes the differentiation of endovascular trophoblasts [130]	Acts as a 'glue' between fetal and maternal tissues by mediating the anchoring of syncytiotrophoblast columns to the decidua [134]	
Laminins	Different isoforms are expressed in the endometrium, changing along with the process of decidualization [93, 94]	Expressed by the trophectoderm, interact with integrins present on endometrial luminal cells [56]	Laminin isoforms influence the direction and quality of invasion of trophoblast cells [95–97]			
Biglycan	Promotes a regular ECM fibrillar organization [31, 32, 36]				Localizes within endothelial and subendothelial cells of the perivascular region of fetal capillaries [24, 147]	
Decorin	Contributes to the differentiation of endometrial stromal fibroblasts into secretory decidual cells [22, 24]		Limits trophoblast invasion through modulation of the availability of TGF-β and the activity of MMPs [8, 24, 111, 116–118]	Interferes with the differentiation into endovascular trophoblasts through VEGFR2 [116]	Is produced by mesenchymal stromal cells of the chorionic villi [24, 145]	Promotes the polarization of decidual macrophages towards a pro-inflammatory M1 phenotype [54]
Perlecan		Expressed by both the trophectoderm and endometrial basal lamina [85]	Facilitates trophoblast invasion and differentiation by modulating the activity of MMPs [62, 86, 87]		Forms a supportive scaffold that maintains the structural integrity of placental tissues [89, 90]	

Table 1 (continued)

ECM molecule	Decidua formation	Embryo apposition / adhesion	Trophoblast invasion	Vascular adaptation	Placental development	Immune modulation
Syndecans	SDC1 promotes endometrial stromal decidualization by binding to osteoprotegerin [152]; SDC1 serves as storage molecule for many chemokines and angiogenic factors [152, 153]	Expressed by the trophectoderm, interact with integrins present on endometrial luminal cells [56]	SDC1 promotes EVT migration into the maternal decidua by interacting with ADAM12 [87, 154]		SDC1 protects the syncytiotrophoblast from oxidative stress and inflammation [87]; interaction of syndecans with PSG1 promotes endothelial tube formation [162]	
Versican	Interacts with other ECM components facilitating the structural remodeling of maternal tissues [124–129]		Promotes trophoblast proliferation and differentiation [124]	Promotes uNK cell proliferation and facilitates the remodeling and dilation of spiral arteries [124]	Supports the formation of syncytiotrophoblast [123, 133]	
Hyaluronan	Peaks of HA deposition are observed during the mid-proliferative and the mid-secretory phase [64–66]	Acts as a linker by binding to CD44 receptors present on both embryo's trophectoderm and endometrial epithelial cells [67]	Trophoblasts secrete large amounts of HA that function in an autocrine manner enhancing their proliferation and migration [70]		Serves as substrate for mesenchymal cell migration; promotes the sprouting of blood vessels [141]	Instructs decidual macrophages to polarize towards an M2 immunosuppressive phenotype [71]

the secretory phase, under the high levels of progesterone released from the corpus luteum, the endometrium transforms into a receptive tissue that is suitable for implantation through a process known as decidualization [18]. In the absence of an embryo, the decidua is shed off through menstruation. On the contrary, when fertilization occurs, the embryo breaches the endometrial luminal epithelium and is rapidly embedded in the decidual stroma [18]. The decidua contributes to early nutrient exchange, production of cytokines, and growth factors as well as supporting the development of new blood vessels, modulates extravillous trophoblasts (EVT) invasion, and acts as a protective barrier against infections and maternal host immune responses. An impairment of decidualization leads to a variety of pregnancy disorders, including infertility, recurrent miscarriages, and uteroplacental disorders [19].

The ECM composition of the endometrium, along with cell-matrix receptor expression, is regulated by sex steroids oestradiol and progesterone throughout the menstrual cycle, giving rise to dramatic shifts in tissue structure and morphology. Cyclical changes in these hormones dictate the timing and functional capabilities of the endometrium to support nidation, through the dynamic remodeling of the ECM [20].

The key event in decidualization is the striking morphological and functional differentiation of human endometrial fibroblasts into specialized decidual stromal cells [21]. Despite being driven by hormones, this process is profoundly affected by microenvironmental cues, among which some ECM components, such as decorin, have been demonstrated to play a key role. Decorin is a small leucine-rich proteoglycan produced by both endometrial stromal cells and decidual cells [22, 23], primarily under the influence of interleukin-1 beta (IL-1β) [24]. During decidualization, decorin is essential for the differentiation of endometrial stromal fibroblasts into secretory decidual stromal cells [24]. Indeed, without decorin, these cells fail to fully differentiate, and exhibit a fibroblastic morphology and a decreased expression of important markers for the initiation and maintenance of decidualization, such as insulin-like growth factor binding protein 1 (IGFBP1) and prolactin (PRL) [25].

Once fully differentiated, decidual stromal cells start secreting a plethora of ECM molecules that induce significant changes in the composition and structure of the endometrial stroma (Fig. 2). A recent targeted proteomic analysis of the endometrial ECM benchmarked the ECM composition along with the menstrual cycle [26]. Gnecco et al. showed that the abundance of ECM glycoprotein fibronectin was greater in the proliferative phase, while collagen and laminin increased during the secretory phase, corresponding to the activity of progesterone (P4) in terms of epithelial gland maturation, vascular

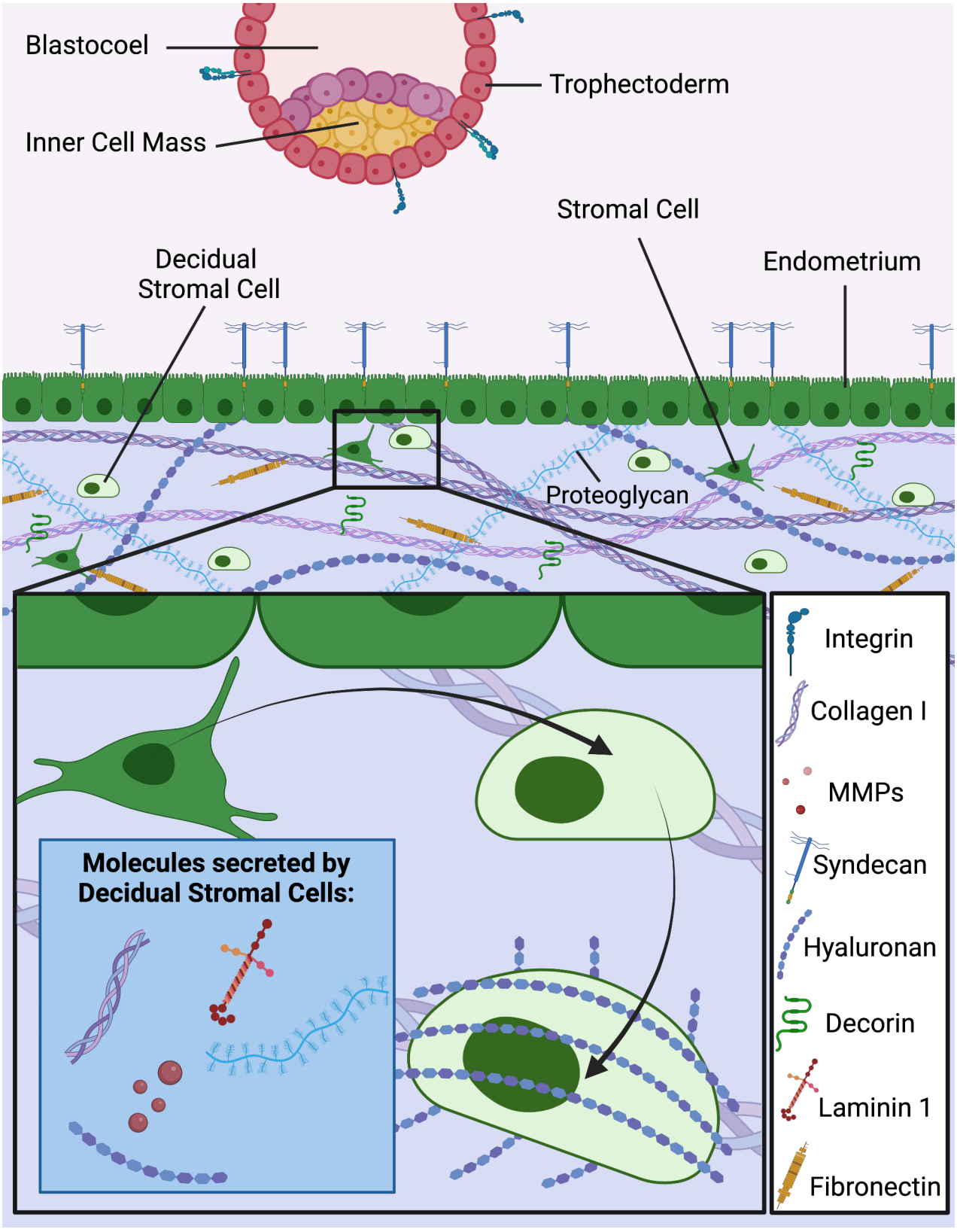

Fig. 2 The image highlights the differentiation of endometrial stromal cells into specialized decidual cells, illustrating the ECM components majorly secreted upon decidualization. Created with Biorender

remodeling and differentiation of stromal fibroblasts [26]. In accordance, the literature pinpoints collagens and fibronectin as the main ECM components remodeled during decidualization.

Collagens

The most represented ECM components of the uterus are collagens, mainly type I, III, IV, V, VI and XVIII [27]. They are primarily produced by decidual stromal cells and organized in a meshwork surrounded by other ECM proteins such as elastin, proteoglycans and glycoproteins [27], as detailed better below. During decidualization, collagens undergo an extensive remodeling that is crucial for the development of a receptive endometrium and the establishment of a healthy pregnancy [28]. An important event in this process is the structural modification of collagen types I, III, and V fibrils, which have been observed to rapidly thicken and rearrange around the decidual cells [29, 30]. The formation of these thick collagen I fibrils is mediated by biglycan, a class I small leucine-rich proteoglycan (SLRP) [31, 32], that in the endometrium is expressed by stromal cells, macrophages, T lymphocytes and endothelial cells [24, 33–35]. In the endometrium, biglycan is present at low levels, whereas its expression increases upon decidualization when it mainly serves as a structural scaffold to promote a regular ECM fibrillar organization [36]. Notably, the volume of these collagen fibres serves as a measurable indicator of decidualization efficacy and has been shown, in mouse models, to correlate with the probability of early pregnancy progression [37].

Among all the collagen types, collagen I is the most represented. It provides biomechanical strength, resilience, structural integrity, and the tensile properties necessary for the normal functioning of the uterus [38]. Its expression changes along with the menstrual cycle and is regulated by many factors, such as progesterone and oestrogen, prostaglandins, nitric oxide, and vitamin D [27]. The epigenetic mechanisms regulating decidual collagen I expression are different, as shown for collagen type I alpha 1 chain (COL1A1), the major component of collagen I together with collagen type I alpha 2 chain (COL1A2). In pregnancy, it has been shown that an aberrant expression of COL1A1, due to the reduction of histone deacetylase 3 (HDAC3) activity or to a low methylation of the promoter of COL1A1, causes a defect of decidualization both in mice and in humans [39, 40].

However, the remodeling of collagen I relies also on other two processes. One is the post-translational modifications catalyzed by lysyl oxidases (LOXs), enzymes that produce intermolecular cross-links between collagen I fibres themselves and other proteins such as collagen III and IV and fibronectin (FN). The other is protein degradation, which is mainly mediated by metalloproteases (MMPs) [41]. The equilibrium between collagen I deposition and degradation is instrumental for uterine tissue integrity and the continuation of a healthy pregnancy, thus loss of this balance may lead to fertility and gestational problems. An increased tissue stiffness is a pathogenic feature of uterine fibroids, while on the contrary, a reduced cervical cross-link density is observed in preterm birth [42]. An excessive tissue stiffness has also been found in the preeclamptic placenta, in which it increases independently from the gestational or maternal age [43].

Other collagens produced by decidual stromal cells are type IV and type XVIII [44, 45]. Collagen IV, one of the major components of basal membranes, is selectively upregulated during the menstrual cycle and decidualization, when its deposition increases around the spiral arteries, highlighting its role in decidual vascular remodeling [45].

Fibronectin

Fibronectin (FN), an important component found throughout the ECM in various tissues of the body, is abundantly present in decidua [46, 47]. Once secreted, FN molecules readily polymerize with each other, forming viscoelastic fibrils that importantly influence cell migration and are essential for processes such as embryonic development and tissue repair [46]. Indeed, the formation of FN fibrils, that typically appear to be stretched within healthy tissues, plays a key role in assembling a provisional ECM during embryonic development and wound healing [48]. Whereas an aberrant fibrils assembly, leading to a more relaxed structure, is often observed in pathologic conditions, such as cancer and fibrosis [49]. In the uterus, FN relaxation has been shown to be dependent on the menstrual cycle. Interestingly, the presence of relaxed FN fibrils is associated with the occurrence of endometriosis, such that they have been proposed as a potential tool for the development of a diagnostic radiotracer targeting endometriotic lesions [50].

During decidualization, FN supports the structural organisation of the evolving ECM by interacting with other stromal proteins, including collagen and proteoglycans, thereby creating a supportive scaffold [51].

Placentation: shaping the ECM to prepare the soil

Overall, ECM remodeling occurring during decidualization is particularly crucial for creating optimal receptive conditions, allowing the following synchronization of functionally appropriate embryo implantation and preparing the ground for blastocyst to adhere and invade the tissue.

Nevertheless, it must be underlined that decidual ECM functions extend beyond providing structural support to the evolving tissues and driving the subsequent trophoblast migration, as detailed in the following paragraphs. Indeed, it actively contributes to the modulation of

immune cell activation during decidualization, which is a process primarily aimed at initiating immunotolerance in the mother towards the foetus. In this context, collagen I has been shown to promote the differentiation of regulatory T (Treg) cells through the inhibition of the Notch1 signaling pathway [52]. Treg cells are a subset of suppressor $CD4^+$ T cells that play a dominant role in the maintenance of immunological self-tolerance, and are essential in promoting fetal survival avoiding the recognition of paternal semi-allogeneic tissues by maternal immune system [53]. In the decidua, collagen I levels correlate negatively with the number of proinflammatory Th17 cells, and positively with the number of immunosuppressive Treg cells, thus confirming its role in shaping an immunotolerant environment [52].

Another ECM component playing a role in immunotolerance is decorin. As stated before, a low level of decorin associates with decidualization defects, however an extremely high deposition of the molecule may negatively affect the occurrence of a physiological pregnancy. In fact, decorin has been shown, by regulating mitochondrial metabolism, to guide macrophage polarization towards a pro-inflammatory (M1) phenotype at the expense of immune-suppressive (M2) cells [54]. Decidual macrophages represent the second largest decidual leukocyte population (20–30%), and are involved in a tight crosstalk with decidual stromal cells [25]. The latter, through the secretion of cytokines as IL-4 and TGF-β, trigger macrophages to acquire an immunosuppressive M2 phenotype. M2 cells, in turn, also affect the functions of decidual stromal cells, and later of trophoblasts, by secreting cytokines, such as IL-10, VEGF-A and TGF-β, that play indispensable roles in decidualization, spiral artery remodeling and trophoblast invasion [25]. We can hypothesize that decorin takes part in this fine-tuned plethora of signals deriving from decidual stromal cells aimed at modulating macrophage polarization to support a correct decidualization. In accordance with this view, an increased decorin level is associated with an imbalanced decidual M1/M2 macrophage ratio and has been demonstrated to promote the occurrence of pregnancy complications such as recurrent pregnancy loss [54].

Apposition and adhesion: matrix to build the bridge

For a pregnancy to be established, initial apposition and adhesion of the blastocyst to maternal endometrium must occur in a coordinated manner. After entering the uterine cavity, blastocyst-stage embryos hatch from the zona pellucida and expose the trophectoderm, the outer layer that represents the primary interface with the endometrial epithelium [55]. The blastocyst orients the inner cell mass proximal against the receptive endometrium, and the trophectoderm of the preimplantation embryo interdigitates with the microvilli called pinopodes present on the surface of the endometrial luminal cells in the apposition phase. Subsequently, changes in the expression of ECM proteins and integrins contribute to the formation of a stable adhesion between the embryo and the maternal tissue [56], as represented in Fig. 3.

Integrins are cell adhesion transmembrane receptors that, by binding to the ECM and the cell cytoskeleton, transduce biochemical and mechanical signals between cells and their environment. Each integrin is a heterodimer that comprises an α-subunit and a β-subunit, bound in a noncovalent complex: 18 α- and 8 β-subunits have been characterized and form 24 functionally distinct heterodimeric transmembrane receptors [57].

The expression of integrins on the endometrial luminal cells is controlled by hormones and cytokines, oestrogen and IL-1 among others, and many integrins have been proposed to play a role in the apposition and adhesion stages of implantation, as $\alpha_v\beta_1$, $\alpha_1\beta_1$, $\alpha_3\beta_1$, $\alpha_6\beta_1$, $\alpha_v\beta_5$, and $\alpha_v\beta_6$ [56, 58]. These receptors interact with the ECM molecules present on the blastocyst, mainly laminins and syndecans, thus acting as a bridge and binding the trophectoderm to the luminal endometrial surface [56, 59].

On the other side, the human blastocyst expresses $\alpha_v\beta_3$ as well as $\alpha_3\beta_1$, $\alpha_6\beta_4$, and $\alpha_v\beta_5$ integrins to further strengthen the adhesion with the endometrial surface. Interestingly, once the blastocyst gets in contact with the soluble factors present in the uterine fluid, as Wnt ligands and LIF, the intracellular trafficking and exposure of specific integrins on the trophectoderm occur [51, 60]. Among others, the exposure of α5β1 integrin on trophectoderm cells allows the interaction with FN present on the luminal layer of the endometrium [60].

The major ECM component playing a role in this phase is hyaluronan.

Hyaluronan

Hyaluronan (HA) is a high molecular weight linear glycosaminoglycan, composed of repeating disaccharides of D-glucuronic acid and N-acetyl glucosamine groups [61]. Despite its simple composition, HA exerts a number of functions, by influencing the hydration and physical properties of tissues, by interacting with other ECM molecules, such as aggrecan and versican, and by binding its cell-surface receptors CD44 and RHAMM. HA participates in many physiological and pathological processes, such as cancer, in which it modulates cell differentiation and migration, immune cell activation and angiogenesis [61–63].

As for other ECM molecules, the levels of HA deposition in the endometrial stroma follow a cyclic fashion. In particular, peaks of HA deposition were observed during the mid-proliferative and the mid-secretory phase. The latter coincides with the time period when implantation

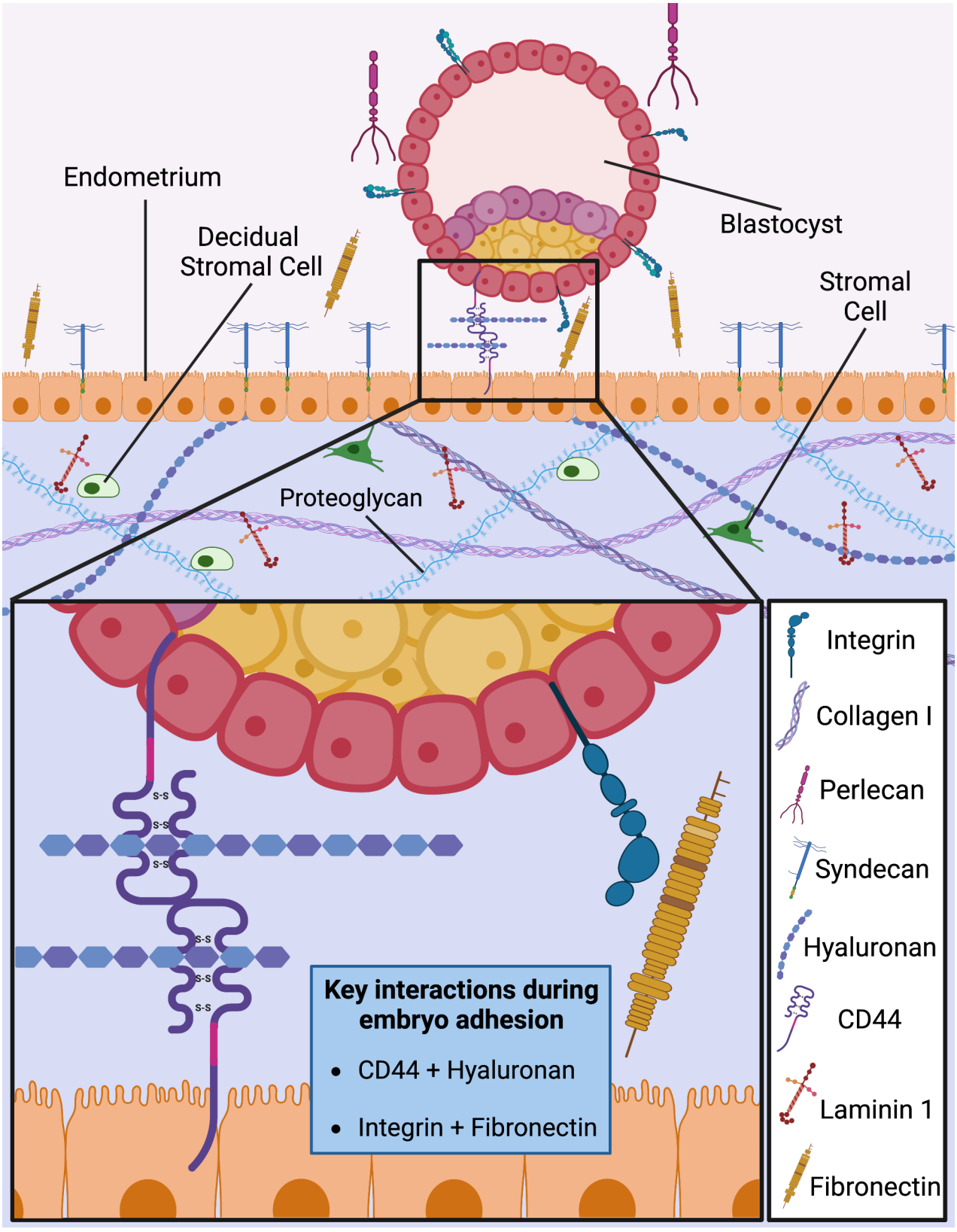

Fig. 3 The illustration represents the main ECM molecules serving as substrate for blastocyst adhesion to the luminal endometrial epithelium. Created with Biorender

of the embryo would be initiated. A perivascular staining for HA was also observed throughout the menstrual cycle, with a higher intensity close to the spiral arteries during the secretory phase [64]. The stage when HA staining is at minimum, prior to menstruation, coincides with the tissue regression, and this is assumed to be a result of the loss of the HA-associated water of hydration [65]. A similar spatio-temporal distribution of HA was demonstrated by Simoes Ricardo Santos et al., who compared healthy women and patients with polycystic ovary syndrome (PCOS), and found that the latter are characterized by an altered HA deposition in association with a dysregulated endometrial cycle [66].

During embryo apposition and adhesion, the production of HA has been demonstrated to increase in the expanded and hatched blastocyst stages [67]. It has been postulated that, in this phase, HA acts as a linker by binding to CD44 receptors present on both embryo's trophectoderm and endometrial epithelial cells, thereby facilitating the initial blastocyst adhesion. The injection of HA during the embryo transfer is nowadays explored as a strategy to improve embryo implantation in IVF cycles [68]. Interestingly, HA is involved in the natural selection of human embryos at implantation [69]. It was demonstrated that low-fitness embryos secrete high molecular weight hyaluronic acid (HMWHA), which, upon binding to CD44 on uNK cells, blocks the targeting and elimination of stressed/senescent cells. This results in sterile tissue inflammation through secondary senescence and menstruation-like breakdown of the endometrium, irrespective of circulating progesterone levels [69].

Despite HA exerts its major function during blastocyst adhesion, it takes part in additional processes along with embryo implantation. It is interesting to note that once trophoblasts start invading the decidua, they begin to secrete large amounts of HA that function in an autocrine manner enhancing the proliferation and migration of trophoblasts themselves [70]. Moreover, trophoblast-derived HA has been observed to instruct decidual macrophages to polarize towards an M2 immunosuppressive phenotype by binding to CD44 and activating the PI3K/Akt-STAT-3/STAT-6 signaling pathways [71], thus contributing to the consolidation of immunotolerance initiated during decidualization.

Trophoblast invasion: on the ECM road

Once the embryo adheres and breaches out the endometrial epithelium, trophoblasts penetrate and invade the uterine wall in a process crucial for a successful implantation and the establishment of a healthy pregnancy. Indeed, an impaired trophoblast invasion associates with pregnancy disorders, such as preeclampsia [72].

The invasive capabilities of trophoblasts depend, on one hand, on the modulation of the expression of integrins that, through the binding with collagens, FN and other ECM proteins, activate the intracellular signaling cascade that drives cell migration [73] (Fig. 4). Integrin expression and exposure on the cellular membrane change along with trophoblast differentiation and function: the proliferative cytotrophoblasts are mostly characterized by the presence of α6β4 and α5β1, whereas the invasive trophoblast switches toward a prominent expression of α1β1 integrin [74]. A peculiar feature of invasive trophoblasts is the transient presence on the cell membrane of αIIbβ3 integrin, that is primarily recognized as a platelet-associated integrin [75]. It has been hypothesized that the exposure of αIIbβ3 on trophoblasts probably results from the fusion with maternal platelet microparticles and mediates the interaction with decidual FN [76, 77]. For its capability to bind also fibrin, Snir et al. have proposed a role for αIIbβ3 integrin also in trophoblast maturation and as a repair mechanism at villous denudations sites, where fibrin deposits may induce trophoblasts proliferation and re-epithelization [77].

On the other side, trophoblast migration occurs through a massive stromal remodeling that relies on the activation of a complex proteolytic machinery [78–82]. Invasive trophoblasts, but also decidual stromal cells and macrophages, express high levels of MMPs, mainly MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MT1-MMP and MMP-26, and urokinase plasminogen activator (uPA) [83, 84]. The expression of these proteases is controlled by many factors, and ECM components as well. This is the case of perlecan, a large heparan sulfate proteoglycan, that plays a crucial role during embryo implantation by facilitating trophoblast invasion and influencing its differentiation [62]. The presence of perlecan in both the trophectoderm and maternal tissues like the basal lamina highlights its importance in mediating interactions between the developing embryo and the maternal environment [85]. Perlecan exerts these functions by modulating the activity of MMPs [86] in a fine-tuned manner necessary to prevent the occurrence of pathologic conditions, like placenta accreta and PE [87, 88]. Interestingly, low levels of perlecan have been found in late-onset pre-eclampsia, while an opposite directional change was observed in early-onset pre-eclampsia, reflecting the distinct placental pathologies of these clinically different pre-eclampsia subtypes [87]. By regulating the activity of MMPs and simultaneously interacting with other ECM components like collagens, fibronectin, and laminin, perlecan contributes to the formation of a supportive scaffold that maintains the structural integrity of placental tissues [89], ensuring balanced invasion for placental anchoring, while preventing excessive invasion [90].

The main ECM components serving as substrates for EVT invasion and migration are laminins, collagens, FN

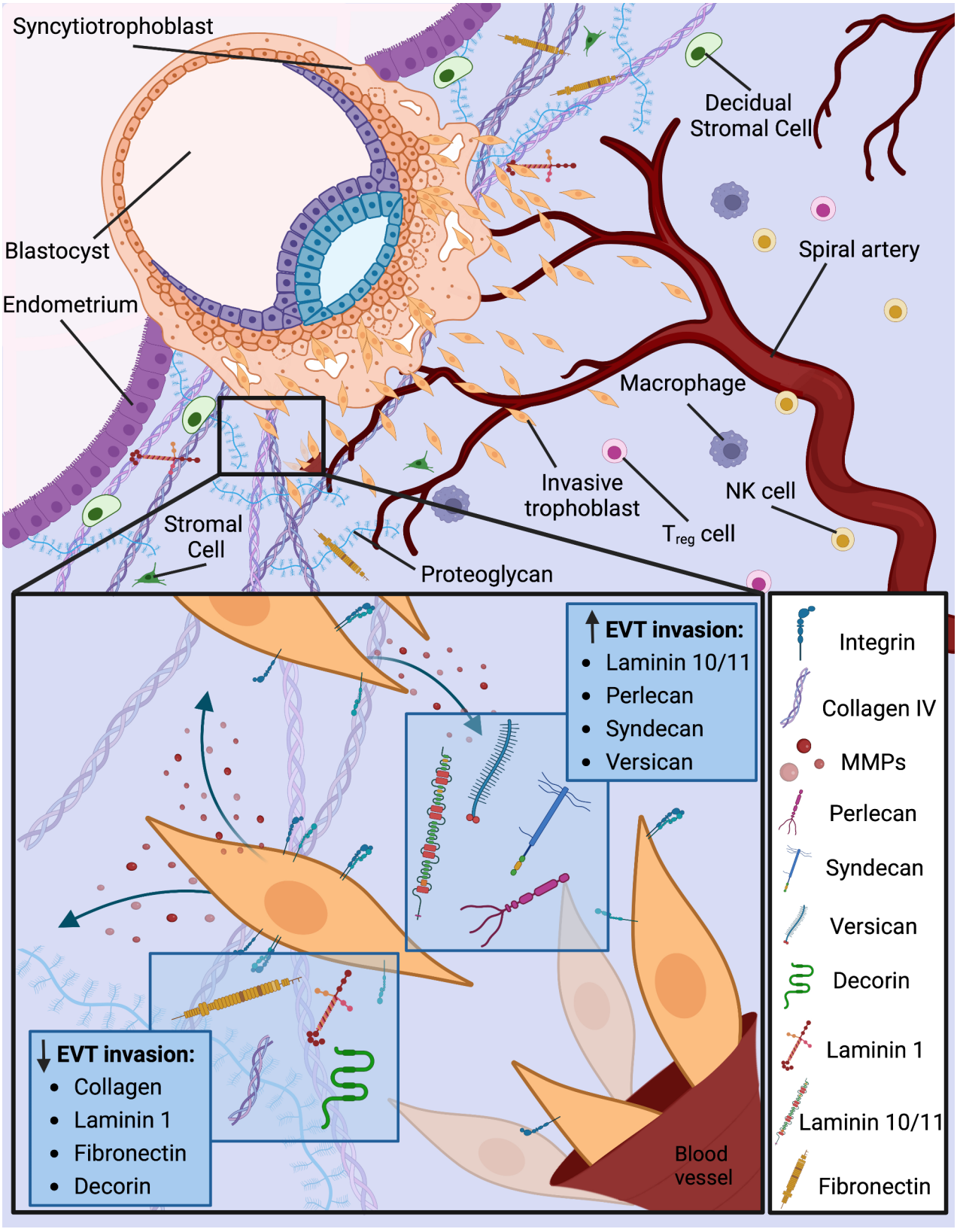

Fig. 4 Key extracellular components involved in EVT migration, which are found to be relevant in the invasion of the maternal decidua during the process of embryo implantation. Created with Biorender

and decorin, as illustrated in Fig. 4 and detailed in the following sections.

Laminins

Laminins are found predominantly in the basement membrane, a thin ECM layer that lines the epithelial and the endothelial sheets, and are structurally composed of three main chains recognized as α, β, and γ which are genetically distinguished and give rise to 15 different known isoforms [91]. Laminins play a crucial role in cell adhesion, migration, survival, and differentiation [3], however they mainly exert adhesive functions. The latter is due to the formation, together with perlecan, of a molecular mesh that gives rise to honeycomb-like networks [92].

Laminins are a critical component of both the trophectoderm basement membrane and the uterine decidual matrix and act as main drivers in the process of embryo implantation. Different laminins isoforms are expressed in the endometrium and they change along with the process of decidualization [93]. In the non-pregnant uterus, laminins 2/4 and 10/11 are present in the basement membrane of the uterine epithelium, and the stromal ECM contains laminins 2/4 and 8/9 [94]. At the onset of implantation, laminins 2/4 and 8/9 expression disappears from the region of the stroma immediately surrounding the implanting embryo, and the stromal decidual cells begin to strongly express laminins 10/11 as they undergo decidualization. These patterns of laminin expression suggest that they may have specific effects on trophoblast function during implantation. Laminins 1 and 10/11 have been shown to exert distinct effects on trophoblast cell behaviour [95]. Laminin 1 promotes random migration and decreases spreading, whereas laminin 10/11 promotes both spreading and persistent migration. When presented as adjacent substrates, cells stop at the boundary and do not enter the region containing laminin 1. In contrast, trophoblast cells maintain strong cell–cell contacts on substrates of laminins 10/11. These effects suggest that these laminin isoforms influence the direction and quality of invasion of trophoblast cells during implantation. In mouse models, a decreased level of laminin 4 and 5 is responsible for the inhibition of trophoblast invasion and vascular adaptation defects, overall leading to a failed implantation [96, 97]. Accordingly, in humans, high levels of these laminins characterize early pregnancy rather than the late stages, thus underlining a modulatory function during trophoblast differentiation and invasion of the decidua. A low level of laminin 4 and 11 has been observed in preeclampsia [96, 98], further strengthening the concept that a tightly regulated expression of laminins is fundamental for a healthy pregnancy to be established.

Collagens

During embryo implantation, collagen type I, together with collagen IV, functions as an adhesive substrate for trophoblasts [99]. An increased collagen I deposition has been shown to suppress trophoblast cell migration and invasion and to associate with the occurrence of preeclampsia [100]. Mechanistically, collagen I induces preeclampsia-like symptoms by suppressing the proliferation and invasion of trophoblasts through the inhibition of the ERK and WNT/β-catenin signaling pathways [101]. Recently, also collagen III has been related to trophoblast migration and its upregulation has been associated with placenta accreta, a gestational disorder referable to an uninhibited trophoblast invasion [102].

Importantly, the proteolytic cleavage of collagen IV and XVIII by MMPs releases biologically active fragments that play a role in early pregnancy events. The degradation of chain α1 of collagen IV generates arresten, which is subsequently detectable in the peripheral blood stream. Intriguingly, arresten levels are significantly increased in plasma during the second and third trimester in women with preeclampsia compared with normotensive [103]. The C-terminal fragment of collagen XVIII, called endostatin, is produced during embryo implantation by the activity of trophoblast-derived MMPs [104]. Interestingly, once released endostatin inhibits trophoblast cell invasion by binding to integrin α5β1, highly expressed by EVT themselves, thus generating a sort of negative feedback loop [105]. In accordance, a high endostatin serum concentration, likely associated with a shallow trophoblast invasion, has been observed in women with preeclampsia [106].

Fibronectin

In the phase of decidua invasion, FN expression is induced in infiltrating EVT in a TGF-β-dependent manner [107, 108]. In turn, FN regulates trophoblast adhesion and migration into maternal tissue through the activation of Erk and Akt signaling pathways. Unexpectedly, a high FN expression has been observed in the placenta of preeclamptic patients and the molecule has been proposed as a useful predictor of preeclampsia development [109]. Several mechanisms have been proposed to explain the elevation of FN levels in preeclampsia, such as vascular injury release, increased FN production, and enzyme degradation, yet the obscure role of FN in the disease remains unclear and debated. Recently, Su and colleagues showed that FN inhibited trophoblast invasion and migration, and that trophoblast-derived FN may function in an autocrine manner by impairing cell motility [110]. Interestingly, the treatment with aspirin, a preeclampsia prevention agent, was able to reduce FN expression as well as its inhibitory effect on trophoblasts.

Further studies will be helpful to better clarify the role of FN alteration in the pathogenesis of preeclampsia.

Decorin

Decorin plays a major role in regulating trophoblast functions by limiting its invasion into the uterine lining [24] and preventing excessive invasion that could lead to complications like preeclampsia [8]. This is achieved through multiple mechanisms. First, decorin binds and stores TGF-β thus preventing its activity until it is cleaved by trophoblast-derived proteases [111]. Since TGF-β exerts an inhibitory function on EVTs migration [112], this mechanism allows the avoidance of uncontrolled over-invasion of the decidua [113]. Additionally, decorin negatively regulates EVT proliferation and migration by binding multiple tyrosine kinase receptors (TKRs) [114]. Interestingly, by binding to vascular endothelial growth factor receptor 2 (VEGFR2) present on the trophoblast cell surface [115], decorin not only interferes with the VEGF-dependent trophoblast invasion, but also with the differentiation into endovascular trophoblast, which is crucial for a proper uterine artery remodeling, as illustrated below [116]. Finally, decorin plays a regulatory role in trophoblast invasion by modulating the activity of MMPs involved in ECM remodeling [117, 118].

Trophoblast invasion: on the ECM road

While EVT massively invades the decidua, a remodeling of the uterine spiral arteries occurs in order to assure the establishment of an optimal blood flow from the maternal to the fetal compartment [119]. This process is possible thanks to the turnover of vascular basal membrane, made by collagen IV, laminins and FN, in a process mediated by the activation of uterine NK cells (uNK) and decidual macrophages [120, 121].

uNKs, abundantly present in the decidua surrounding spiral arteries, importantly contribute to vascular adaptation by inducing the separation of vascular smooth muscle cells and the degradation of the vascular ECM via the secretion of MMPs, Ang1, Ang2, VEGF-C, and IFNγ [122]. The recruitment and proliferation of uNK are mainly triggered by stimuli derived from EVT, but are also affected by ECM molecules, among which versican, a large chondroitin sulfate proteoglycan. Versican exerts multiple functions in various pregnancy-related processes [123, 124]. It is known to interact with other ECM components, mainly hyaluronan, playing an important role in the formation of the provisional matrix [125], that in the early phases of pregnancy may favour the structural remodeling of maternal tissues necessary for the development of the fetus. Five versican isoforms have been described in mammals: V0, V1, V2, V3 and V4. In the endometrium, V0, V1, and V3 isoforms are expressed under the control of progesterone, among other hormones, thus changing along with the menstrual cycle and pregnancy [126], with increasing levels during the secretory phase in preparation for embryo implantation [127, 128]. During the window of implantation, the deposition of isoforms V1 and V0 strongly increases in endometrial tissue [129], and acts by promoting trophoblast proliferation and differentiation [124]. These higher levels of versican are also functional to promote uNK cell proliferation and to facilitate remodeling and dilation of spiral arteries [124]. Despite the molecular mechanisms have not been uncovered yet, the relevance of versican in vascular adaptation is emphasized by the observation that, in mouse models, its deletion leads to the formation of arteries characterized by a thick vessel wall and a narrow lumen, overall resulting in the occurrence of maternal hypertension and fetal growth restriction (FGR) [124].

Simultaneously with arterial vessel remodeling, a specialized type of trophoblast, called endovascular trophoblast, differentiates and migrates upstream along the arterial wall, replacing the endothelium and contributing to the disruption of the muscular lining of the arteries. In this context, Lan et al. demonstrated that FN expression, further induced by the secretion of trophoblast-derived Activin A, promotes trophoblast migration and the acquisition of the endothelial-like phenotype [130]. Accordingly, the depletion of FN in in vivo models results in an attenuated endovascular trophoblast migration and a halted decidual vascularization, overall interfering with early embryo implantation [130].

During invasion, endovascular trophoblast penetrates the maternal spiral arteries and forms temporary "plugs" in the lumen of the vessels, decreases the flow of maternal blood, thus establishing an oxygen gradient between the mother and fetus, essential for differentiation, growth, and development of the placenta [131].

Placentation: how to draw a forest with the matrix

Once the embryo implants completely into the uterus, the proliferation and differentiation of trophoblasts provide the basis for the process of placentation [132], in which the ECM plays multifaceted roles (Fig. 5). Trophoblasts that face directly the maternal tissue differentiate and fuse to form the syncytiotrophoblast, that will represent the interface between mother and fetus for nutrient transport and gas exchange, whereas those remaining behind, that act as a rapidly dividing stem cell pool, do not fuse and are denominated cytotrophoblasts. In this phase, a particular role can be attributed to the expression of specific isoforms of versican. The secretion of V0 and V1 isoforms is specifically induced in syncytiotrophoblasts, whereas they are scarcely expressed by cytotrophoblasts, and the presence of this molecule in the environment is necessary for a proper syncytialization,

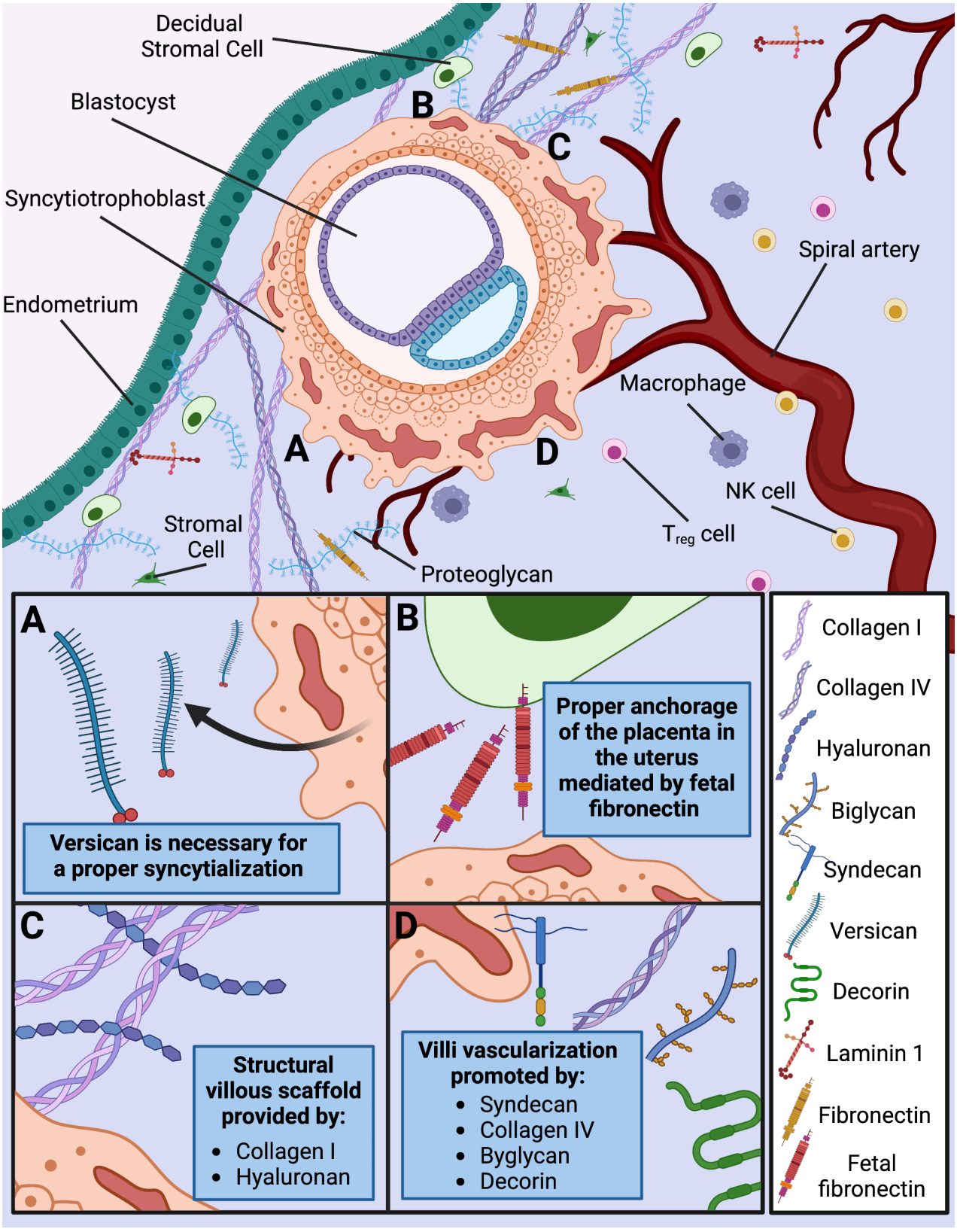

Fig. 5 In the beginning of placentation, the differentiation of syncitiotrophoblast occurs and precedes the formation of the villous tree. In the illustration the ECM molecules relevant in this phase are indicated. Created with Biorender

thus acting as an autocrine factor [123]. Indeed, in vitro studies have assessed that versican silencing in BeWo cells, a trophoblast cell model, induces cell death and a defective syncytial fusion, and also relates with a lower production of human chorionic gonadotropin (hCG). Following this evidence, a lower versican deposition has been associated with pregnancy complications like gestational trophoblastic diseases (GTD) [123, 133].

Upon the formation of syncytiotrophoblast, fluid-filled spaces coalesce and rearrange into lacunae within the syncytium [132]. While invasion evolves, columns of the syncytiotrophoblast masses establish a network around the lacunae to form trabeculae, very important for the remaining development of the villous tree. The formation of syncytiotrophoblast columns is functional for a proper anchorage of the placenta in the uterus. This tight anchorage is mainly mediated by the deposition of fetal fibronectin (FFN) [134]. FFN is concentrated in the area between decidua and trophoblasts and acts as a 'glue' between fetal and maternal tissues. As pregnancy progresses, the distribution of fibronectin changes: it is heavily present in the endothelial cells of fetal blood vessels, lightly present in the stromal fibroblasts, and no longer expressed in the basement membrane of the trophoblast [47]. Normally very low levels of FFN can be found in secretions of the vagina and cervix. Raised levels of FFN after 22 weeks of gestation, likely due to the disruption of the fetal-maternal interface and release of fetal matrix molecules, are a recognised marker to identify women who are at a high risk of preterm birth [135, 136]. Various studies have investigated FFN utility as a potential plasma biomarker also for PE, even if its accuracy and validity as a predictor of this disease still remain debatable. On the contrary, it has been demonstrated that the amount of FN loaded in the placenta-derived small extra-cellular vesicles (sEVs) extruded into the maternal circulation is markedly elevated in preeclamptic placenta and it could serve as an early molecular signature for the detection of the disease onset [137, 138].

As the trophoblast shell gradually begins to break open, maternal blood is permitted to enter the placental lacunae originating the early uteroplacental circulation, and the placenta villous starts to develop [139]. Mesenchymal villi are the most primitive type of villi, they have a loose stroma, and fetal capillaries are poorly developed. Originating from mesenchymal villi, villous sprouts form and transform into immature and mature intermediate villi and terminal villi, grape-like structures characterized by a high degree of capillarization and highly dilated sinusoids. Terminal villi represent the functional unit of the placenta, and their structure grants the optimal environment for efficient diffusive exchange between the mother and fetus. Along with villous formation, the fetal vascular system differentiates into villous capillaries [139].

The placental villous microenvironment surrounding fetal capillaries is composed primarily of fibroblasts, myofibroblasts, macrophages (Hofbauer cells), and ECM. The majority of villous stroma is synthesized and deposited by villous fibroblasts, and is crucial to provide physical and bio-chemical support to the evolving tree [132].

The structural villous scaffold is primarily provided by collagen I. Along the villous tree, an uninterrupted structure of collagen I fibres has been observed [140]. Notably, these fibres are organised differently according to the various levels of villous branching. The collagen of stem villi, emerging from the chorionic plate, forms numerous fibres: the external ones, facing the villous surface, are mainly arranged longitudinally, while the ones in the central core dispose concentrically around the wall of the fetal vessels. The extent of collagen deposition decreases in the free terminal villi, which show a scarce amount of collagen arranged in thin concentric layers within the villous core, surrounding numerous dilated capillary and sinusoid spaces [140]. This collagen I distribution is meant to ensure the most favourable microenvironment for feto-maternal exchanges while providing support to the villous tree.

The formation of the placental villous tree is accompanied by a marked presence of HA, detectable in the stroma of mesenchymal and immature intermediate villi [141]. These significant amounts of HA are needed to serve as a substrate for mesenchymal cell migration and for the sprouting of blood vessels. Being an important component of the endothelial glycocalyx, a vasoprotective barrier between the blood and endothelium, HA also plays a key role in determining the vascular homeostasis within the placental villi [141]. Considering this evidence, we can envision that an altered deposition of HA might occur during PE pathogenesis, even if this aspect still remains poorly studied and debated [142, 143].

In addition to HA, other molecules known to influence vascularization and vessel homeostasis are present in the stroma of the villi, as collagen IV, decorin and biglycan [24, 144, 145]. The latter, in particular, localises within endothelial cells and subendothelial cells of the perivascular region of fetal capillaries [24], however its function in this site is still unknown. Provided that biglycan regulates angiogenesis and vascular development in cancer [146], its role in the process of placentation might be relevant and deserves to be better delineated. In line with this vision, a low biglycan expression has been observed in the placenta of pregnancies with FGR, and it has been hypothesized that a low biglycan deposition may contribute to this condition by promoting thrombosis or vascular structural alterations [147].

A peculiar role in placentation and fetal vessel sprouting may be attributed to Heparan Sulfate Proteoglycans (HSPGs) or syndecans, transmembrane proteins involved

in intercellular signaling, tissue morphogenesis, and cell adhesion [148].

Syndecans

The syndecan (SDC) family consists of four members: SDC-1 (CD138), SDC-2 (fibroglycan), SDC-3 (N-syndecan), and SDC-4 (amphiglycan) [149, 150]. They are mostly expressed on the surface of epithelial cells and exhibit a distinct and tightly controlled expression pattern. In reference to the human placenta, only SDC1, SDC2, and SDC4 are detectable. In particular, SDC1 and SDC2 are predominantly expressed by syncytiotrophoblasts, and in all trophoblast and mesenchymal lineages, respectively, while SDC4 is detectable in extravillous trophoblast and villous cytotrophoblasts during early pregnancy [151].

Although most of the data in the literature indicate that syndecans play an important role in placentation, they are also known to affect earlier events. Indeed, during decidualization, SDC1 functions as a co-receptor for osteoprotegerin, a cytokine receptor of the tumour necrosis factor receptor superfamily, and this interaction promotes endometrial stromal decidualization [152]. At the same time, SDC1 serves as a storage molecule for many chemokines, such as CXCL1 and CXCL8, and angiogenic factors, as HGF and IL-8, which are essential for a successful implantation [153, 154]. Interestingly, the loss of SDC1 expression in endometrial stromal cells has been shown to reduce their sensitivity to the apoptotic cell death driven by embryonic stimuli, a necessary mechanism for successfully establishing a pregnancy [155]. In later phases, during the invasion process, SDC1 promotes EVT migration into the maternal decidua by interacting with the metalloproteinase ADAM12 [87].

In the placenta, SDC1 is found on the extracellular luminal surface of epithelial cells and syncytiotrophoblasts as a major component of the glycocalyx [156]. SDC1 is important in preserving the structural integrity of the placental barrier and may protect the syncytiotrophoblast from oxidative stress and inflammation, crucial for a healthy pregnancy [87]. In agreement, a reduced expression of SDC1 on the syncytiotrophoblast of placental villi has been observed in gestational diseases, as PE [157]. A soluble form of SDC1, which is shed from the cell surface, can further influence the placenta and the systemic maternal health during pregnancy by acting as an autocrine or paracrine signaling mediator and as a competitor of transmembrane SDC1 [87, 157]. Moreover, since the enzymatic digestion of glycocalyx components has been shown to reveal endothelial adhesion molecules and facilitate leukocyte-endothelial interactions [158], we can assume that SDC1 shedding might also impact immune cell trafficking within the placenta. The soluble form of SDC1 is normally present in the serum of pregnant women, but its levels are lower in the case of PE and fetal growth restriction [157, 159]. It is interesting to note that the decreased SDC1 concentration is observed before the clinical onset of PE, suggesting a role for glycocalyx disturbance in the pathophysiology of the disease [157].

During syncytialization, whereby cytotrophoblasts fuse to form the syncytiotrophoblast, syndecans mediate cell-cell and cell-extracellular matrix interactions and cell signaling. This is achieved mainly through the direct binding with growth factors, as HGF, VEGF-A and FGF, or by functioning as co-receptors [160, 161]. A notable example is the interaction of syndecans with pregnancy-specific β1 glycoprotein (PSG1), secreted by the syncytiotrophoblast which has been shown to induce endothelial tube formation through binding to glycosaminoglycan chains on cell surface proteoglycans [162]. The binding of PSG1 to syndecans on endothelial cells in the placenta, together with the ability of PSG1 to induce TGF-β_1 and VEGF-A by immune cells and trophoblasts, further mediates the proangiogenic activity of these proteins [162].

Syndecans can also act as independent receptors. Specifically, CXCL4, a small protein released from activated platelets, binds to syndecans through their glycosaminoglycans chains within the endothelial glycocalyx, increasing vascular permeability and facilitating leukocyte recruitment and adhesion to the vascular endothelium [163]. Since CXCL4 has been found in placental villi, likely deriving from maternal platelets adhering to the villous surface [164], we can assume that the interaction between CXCL4 and syndecans might play a similar role also in placentation.

Conclusions and opportunities

There is mounting evidence that, during the tissue remodeling evoked along with decidualization, embryo implantation and placentation, the ECM undergoes massive modifications in both its structural and biochemical features. These changes are functional for the establishment of a receptive endometrium and efficient trophoblast invasion, key for a physiological pregnancy to occur. Indeed, several ECM components have been shown to play a role in the modulation of blastocyst adhesion and EVT migration.

A proficient remodeling of the ECM is so essential in this context that its alteration is associated with the occurrence of gynaecological and pregnancy diseases, as adenomyosis, preeclampsia and placenta accreta [11, 12, 165]. Preeclampsia is a frequent gestational disorder that often leads to fetal growth restriction and whose pathogenesis relies on a shallow trophoblast invasion and an incomplete remodeling of the spiral arteries [12]. As highlighted in this review, in preeclamptic pregnancies

many ECM molecules are aberrantly expressed, among them collagens, FN, laminins and proteoglycans. It is conceivable to hypothesize that their dysregulation is not a mere consequence of the altered processes of embryo implantation, but that it might concur with the pathogenesis of the disease, even if more work is needed to fully understand the mechanisms behind.

In this regard, studies performed in other contexts may lend a hand and be a source of new hypotheses. The cellular and molecular processes influenced by ECM components have been deeply investigated in cancer, in which a high relevance has been attributed to tumor-specific stromal remodeling. Provided that invasion processes related to tumor growth and embryo implantation share many common features, it is conceivable to hypothesize that the function identified for a specific molecule in cancer deserves to be investigated in pregnancy. For instance, much evidence pinpoint decorin and perlecan as major regulators of tumor angiogenesis [166–171], however their contribution to the process of decidual vascular adaptation and placental vascularization is still poorly described. In addition, there are many ECM molecules that play an important role in tumors about which little or nothing is known in the context of pregnancy [3, 6]. This is the case of tenascin-C, a key modulator of vascular and immune cells in cancer, whose role in mediating the crosstalk between macrophages and endothelial cells has recently been described [172]. Despite the relevance of these two cell types in pregnancy, tenascin-C remains poorly investigated in pregnancy, even if it has been found altered in preeclampsia and in high-risk pregnant women [173, 174].

Other key ECM components still unexplored in pregnancy are EMILINs, a family of glycoproteins exerting multiple functions in physiological and pathological conditions. It is known that EMILIN1 is produced by decidual stromal and smooth muscle uterine cells, and forms a gradient of increasing concentration in the perivascular region of modified vessels, likely guiding trophoblasts invasion [175]. Being important for lymphatic vessel functionality [176, 177], we can envision that EMILIN1 should be further investigated in the process of lymphatic mimicry, defined as the expression of lymphatic markers by spiral artery endothelial cells, which is known to play a physiological role during spiral artery remodeling and is necessary for efficient placentation [178]. Since EMILIN1 has been shown to form macromolecular structures together with EMILIN2 [179], an important protein exerting angiogenic and immunomodulatory functions in tumors [5, 180–182], we believe that a comprehensive analysis of these two molecules would provide further insights on several early pregnancy processes.

A better understanding of the mechanisms driven by ECM molecules would also be crucial considering that stromal remodeling represents a world to be explored for the identification of novel molecular markers for infertility and pregnancy diseases. Indeed, several proteolytic enzymes targeting ECM components and their inhibitors are nowadays emerging as serologic markers of preeclampsia [183–185] and we believe that, in this regard, also the serum levels of ECM-derived fragments in the peripheral blood should be considered as valuable markers for endometrial and placental stromal alterations [4].

Additionally, it may be speculated that, in the future, ECM remodeling may be investigated as a therapeutic target for infertility and pregnancy disorders. In this view, few but promising breakthroughs have been made. Among them, the administration of collagenase-1 has provided consistent and significant evidence of efficacy in the promotion of endometrial ECM remodeling by degrading collagens and proteoglycans and releasing matrix-bound bioactive factors, leading to an efficient enhancement of uterine receptivity and embryo implantation in pre-clinical mouse models [186]. Overall, we highly emphasize the dire need for a better understanding of the functions of the ECM components at the maternal-fetal interface in the progression of healthy pregnancies as a pressing issue to guide efforts to improve the management of obstetric diseases.

Abbreviations

COL1A1	Collagen Type I Alpha 1 Chain
COL1A2	Collagen Type I Alpha 2 Chain
ECM	Extracellular Matrix
EVT	Extravillous Trophoblasts
FFN	Fetal Fibronectin
FGR	Fetal Growth Restriction
FN	Fibronectin
GTD	Gestational Trophoblastic Diseases
HA	Hyaluronan
hCG	Human Chorionic Gonadotropin
HDAC3	Histone Deacetylase 3
HMWHA	High Molecular Weight Hyaluronic Acid
HSPGs	Heparan Sulfate Proteoglycans
IGFBP1	Insulin-like Growth Factor Binding Protein 1
IL-1β	Interleukin-1 beta
LOXs	Lysis Oxidases
MMPs	Metalloproteases
P4	Progesterone
PCOS	Polycystic Ovary Syndrome
PGs	Proteoglycans
PRL	Prolactin
sEVs	Extra-cellular Vesicles
SLRP	Small Leucine-rich Proteoglycan
TE	Trophoectoderm
TKRs	Tyrosine Kinase Receptors
uNK	Uterine NK Cells
uPA	Urokinase Plasminogen Activator
VEGFR2	Vascular Endothelial Growth Factor Receptor 2

Author contributions

F.R. conducted the literature review, designed the figures, prepared Table 1 and wrote part of the manuscript. S.L. conducted the literature review, prepared Table 1 and wrote part of the manuscript. A.F. conducted the literature review and wrote part of the manuscript. E.G designed the figures, prepared Table 1 and revised the manuscript. E.A. conducted the literature

review, wrote and revised the manuscript and supervised the process. G.R. revised the manuscript and supervised the process.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study did not require ethical approval or patient consent. All analyses were performed according to previously published studies.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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