Chapter 8
Hypoxia: A Potent Regulator of Angiogenesis Through Extracellular Matrix Remodelling

Katerina Karavasili and Pieter Koolwijk

Abstract Angiogenesis, sprouting of new vessels from pre-existing ones, occurs throughout life in both health (physiological angiogenesis) and disease (pathological angiogenesis). The process of angiogenesis is regulated by a delicate balance of pro- and anti-angiogenic stimuli including cell–cell interaction by endothelial cells and bystander cells, production of growth factors and their inhibitors, and the modulation of the extracellular matrix (ECM). One of the driving forces of angiogenesis is the shortage of oxygen (hypoxia) occurring in the tissues. Hypoxia regulates the production of many angiogenic growth factors but also stimulates cells to express proteins of the matrix and enzymes that modify the matrix. Here, we describe the effect of hypoxia on the modification of the ECM components. We particularly focus on the synthesis and modification of collagens, the major ECM molecules that dictate the physical and biochemical properties of the ECM. Finally, we discuss further clinical interest that might be hopeful in aberrant angiogenesis or/and hypoxic conditions that characterize many diseases (e.g. diabetes, cancer).

8.1 Introduction

New blood vessel formation includes (a) vasculogenesis that refers to de novo formation of new vessels; (b) arteriogenesis, during which pre-existing vessels enlarge and mature, e.g., the remodelling of arterioles or collaterals into large high flow vessels; and (c) angiogenesis during which new capillaries derive from pre-existing vessels (Semenza 2007). Angiogenesis occurs throughout life in both health (physiological angiogenesis) and disease (pathological angiogenesis). During development, angiogenesis is required for the normal formation and function of a

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living organism. In the adult, physiological angiogenesis is limited and can be only enhanced during wound healing and the menstrual cycle. Pathological angiogenesis, on the other hand, is a major contributor to diseases such as cancer (Hanahan and Folkman 1996; Lugano et al. 2020; Zuazo-Gaztelu and Casanovas 2018), diabetic retinopathy (Capitão and Soares 2016; Patel et al. 2005), age-related macular degeneration (Yamamoto-Rodríguez et al. 2020), rheumatoid arthritis (Elshabrawy et al. 2015), endometriosis and psoriasis (Folkman 2006; Heidenreich et al. 2009).

In the blood vessel wall, three major cell types can be distinguished. A monolayer of endothelial cells is found towards the luminal surface of the vessels and sits on a basal lamina (basement membrane, BM), which is a thin and flexible sheet of extracellular matrix (ECM). In capillaries, scattered pericytes are wrapped around the BM, providing growth factors and cytokines that regulate functions of blood vessels and contribute to their stabilization. The wall of larger blood vessels, such as veins and arteries, are thicker and besides the BM, also contain one or more layers of smooth muscle cells and connective tissue (Ho-Tin-Noé and Michel 2011; Caporali et al. 2017; Marchand et al. 2019; Méndez-Barbero et al. 2021).

The first step in angiogenesis is the signal that comes from injury or disease characterized by a reduced oxygen level, often called hypoxia. Hypoxia upregulates the expression of several genes, including angiogenic growth factors, such as vascular endothelial growth factor A (VEGFA) that is relatively selective for endothelial cells. These angiogenic growth factors activate endothelial cells via binding to specific receptors on their cell surface. Initially, the pre-existing blood vessels vasodilate due to the production of nitric oxide (NO) and become hyperpermeable. In addition, the endothelial cells start to produce new molecules, including enzymes that degrade the BM, e.g. matrix metalloproteinases (MMPs) and members of the plasmin system. Partial degradation of the surrounding matrix facilitates the migration towards the stimulus (diseased tissue, tumour) and the proliferation of endothelial cells. Finally, the newly formed vessel tubes are stabilized by the synthesis of new BM, by recruiting supporting cells, such as pericytes and smooth muscle cells, and blood flow begins (Fong 2008; Senger and Davis 2011; Fraisl 2013; Schito 2019).

Under physiological conditions, the dynamic process of angiogenesis is strictly regulated by the co-ordinated function of numerous angiogenic stimulators and inhibitors that include growth factors, proteases and protease inhibitors, cytokines, and chemokines. This balance is disturbed in pathological conditions that are characterized by low pO_2 and/or low pH, such as hypoglycaemia, mechanical stress, injury, inflammation, and cancer. In such cases, the effect of the stimulators exceeds that of the inhibitors and there is a dramatic increase in endothelial cell activity, a phenomenon known as “the angiogenic switch”.

Hypoxia is one of the major drivers of angiogenesis. When oxygen levels drop in inflamed tissues or tumours, either by an inadequate blood supply or an increased oxygen demand, a transcriptional response to hypoxia ensues. Among other transcriptional pathways that may also be activated, the major transcription pathway involved is that of the hypoxia-inducible factors (HIFs). HIFs have been shown to bind to a cis-acting hypoxia-response element in numerous genes that encode

angiogenesis regulators, such as VEGFA, angiopoietin-2 (ANGPT2), platelet-derived growth factor beta (PDGFB), and fibroblast growth factor 2 (FGF2), and many others (Hickey and Simon 2006; Hirota and Semenza 2006; Gilkes et al. 2014).

In the present review, we describe the effect of hypoxia on the modification of angiogenesis-related ECM components, focusing on the synthesis and modification of collagens, the major matrix molecules that dictate the physical and biochemical properties of the ECM. Finally, we discuss further clinical interest that might be hopeful in aberrant angiogenesis or/and hypoxic conditions that characterize many diseases (e.g. diabetes, cancer).

8.1.1 Hypoxia Signalling Pathways

Hypoxia-inducible factors (HIFs) are heterodimeric transcription factors that consist of an oxygen-regulated HIF-α (HIF1α, HIF2α, and HIF3α) subunit and a constitutively expressed HIF-β subunit (Wang et al. 1995; Wang and Semenza 1995). In normoxia, hydroxylation of two proline residues (at positions 402 and 564) and acetylation of a lysine residue of HIF-α promote its interaction with the von Hippel-Lindau (pVHL) ubiquitin E3 ligase complex (Masson et al. 2001) that ubiquitinates HIF-α, which is then degraded in the proteasome (Fig. 8.1). Prolyl hydroxylation of HIF-α is catalysed by HIF prolyl hydroxylase domain-containing protein 1 (PHD1), PHD2, and PHD3, in a reaction that is dependent on oxygen, Fe^{2+}, and α-ketoglutarate (Epstein et al. 2001; Kaelin and Ratcliffe 2008). Hydroxylation of an asparagine residue of HIF-α can also take place and inhibits its transcriptional activity (Lando et al. 2002). Under low oxygen conditions, HIF-α hydroxylation, ubiquitination and degradation is inhibited (Semenza 2012), and thereby a HIF-α stabilization and accumulation occurs in the cell (Fig. 8.1).

The mechanisms through which hypoxia regulates angiogenesis are not entirely elucidated. It is well known that hypoxia, via HIF-α activation, rapidly induces VEGFA mRNA expression in all types of cells, and is the major mechanism through which hypoxia induces angiogenesis. However, hypoxia activates both HIF1α and HIF2α that although have several overlapping functions, also have distinct target genes and functions, adding to the complicated transcriptional response of endothelial cells to hypoxia (Nauta et al. 2017). Overall, HIF1α seems to induce the formation of tortuous and leaky vascular structures that are not adequately perfused, while HIF2α that is abundantly expressed in endothelial cells seems to induce the stabilization of new vessels (Skuli et al. 2012; Gong et al. 2015; Nauta et al. 2016).

Hypoxia is traditionally classified into acute and chronic that may differentially affect gene expression (Bayer et al. 2011). Acute hypoxia is mainly caused by temporary, local disturbances in tissue perfusion (Bayer et al. 2011) and has been shown to enhance the expression of the urokinase-type plasminogen activator receptor (uPAR), which—in part—explains the initial increased angiogenic response of endothelial cells, as demonstrated by the increased formation of

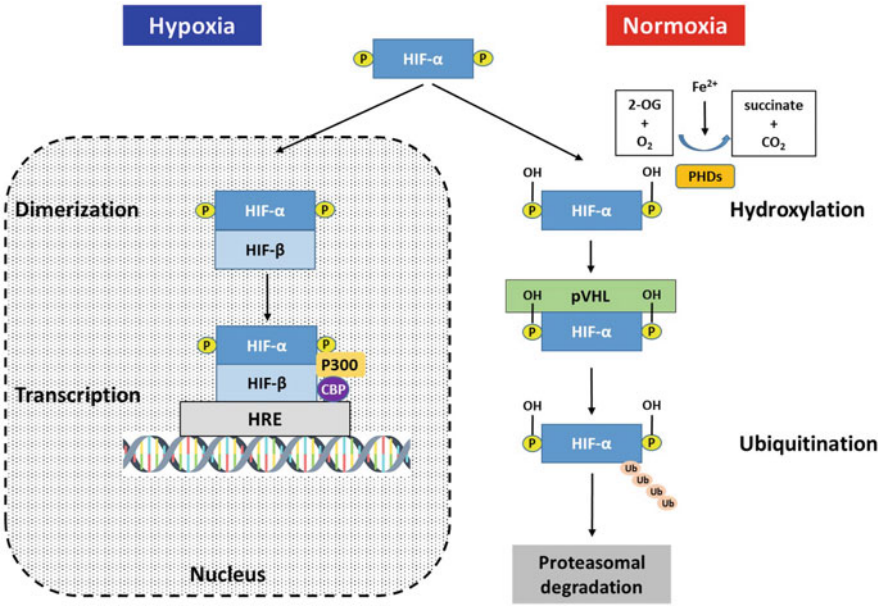

Fig. 8.1 Oxygen-dependent regulation of HIF-α stabilization and transactivation. In normoxia (right), hydroxylated HIF-α proteins bind to the E3 ubiquitin ligase VHL complex (pVHL), leading to its degradation by the proteasome. In hypoxia (left), the activity of PHDs is reduced due to lack of O_2, leading to HIF-α stabilization. CBP and p300 are co-activators that are required for transcriptional activation

capillary-like tubular structures in 3D fibrin matrices (Kroon et al. 2000). Chronic hypoxia lasts relatively long and can stop cell proliferation in the oxygen-depleted regions (Bayer et al. 2011; Saxena and Jolly 2019). It has been suggested that HIF1α predominates in acute hypoxia, whereas HIF2α is mostly responsible for responses to chronic hypoxia (Henze and Acker 2010), such as a more aggressive tumour phenotype through activation of genes such as MMP9, plasminogen activator inhibitor 1, or a 3.5-fold induction of the *Vegfa* gene (Weigand et al. 2012). On the other hand, HIF2α target genes that inhibit endothelial sprouting, such as peroxisome proliferator-activated receptor γ and membrane metalloendopeptidase, have also been found up-regulated during prolonged hypoxia in vitro (Nauta et al. 2017), supporting a shift towards a less aggressive phenotype.

8.1.2 The Structure and Function of the ECM

The ECM is a highly dynamic network that besides its structural role, it also regulates cellular functions dependent on its rigidity/elasticity and its composition. ECM continuously undergoes remodelling that is co-ordinated by the balance

between production of new matrix components and degradation by matrix-degrading enzymes. Deregulation of such balance and changes in ECM composition associates with the development of several pathological conditions (Bonnans et al. 2014; Kastana et al. 2019; Mongiat et al. 2019; Yanagisawa and Yokoyama 2021; Kretschmer et al. 2021; Haller and Dudley 2022; Miller and Sewell-Loftin 2022).

The ECM varies between species and between tissues and is composed of structural biomolecules such as collagens, laminins, elastin, fibronectin, glycosaminoglycans (GAGs: hyaluronate, keratan sulphate, chondroitin sulphate, dermatan sulphate, and heparan sulphate), and proteoglycans. Most of these ECM molecules are synthesized and secreted locally by resident cells, among which endothelial cells. In addition to ECM structural components, there are other non-structural proteins called "matricellular" proteins that function as adaptors and modulators of cell–matrix interactions to guide ECM synthesis (Bonnans et al. 2014; Mongiat et al. 2019; Gopinath et al. 2022).

8.2 Hypoxia-Induced Changes in the ECM

The effect of hypoxia on ECM remodelling is long known and follows the effect of hypoxia on the transcription of numerous genes and on cell functions, such as cell proliferation and migration. For example, hypoxia seems to affect fibroblast proliferation to a great degree, so that fibrosis is considered an important outcome of tissue hypoxia (Darby and Hewitson 2016; Xiong and Liu 2017; Valle-Tenney et al. 2020; Foglia et al. 2021; Romero and Aquino-Gálvez 2021). Hypoxia also stimulates vascular smooth muscle cell proliferation and collagen deposition, thus contributing to pulmonary vascular remodelling (Jeffery and Morrell 2002) mediated by endogenous transforming growth factor beta (TGFβ) (Chen et al. 2006) and reversed by ECM remodelling inhibition (Jeffery and Morrell 2002). Remodelling of the ECM following hypoxia has also been considered, at least partly, responsible for the cardiac dysfunction induced by sleep apnoea (Farré et al. 2018), tumour progression and metastasis (Labrousse-Arias et al. 2017), the stemness and differentiation potential of cancer stem cells involved in vasculogenic mimicry (Wei et al. 2021), and for angiogenesis (Germain et al. 2010; Rodriguez et al. 2021).

8.2.1 Hypoxia Effect on Collagen Gene Expression

Collagens, as major and abundantly expressed ECM proteins, provide tensile strength, regulate cell adhesion, support chemotaxis and migration, and direct tissue development. Among the numerous types of collagens, the main types of fibrillar collagens I, II, III, V, XI, and XXIV are found in connective tissues, whereas the networking collagens IV, VIII, and X are predominately found in the BM of epithelial and endothelial cells (Ricard-Blum 2011).

Numerous in vitro and in vivo studies have shown an increased rate of collagen synthesis under hypoxic conditions by fibroblasts (Norman et al. 2000; Liu et al. 2019; Kang et al. 2020), renal epithelial cells (Basu et al. 2011; Rozen-Zvi et al. 2013), and in hepatic stellate cells (Corpechot et al. 2002), contributing to tissue fibrosis, while at the same time it also stimulates angiogenesis (Corpechot et al. 2002). In most of the published data, it is not clarified whether hypoxia has a direct effect on collagen transcription, while there are some studies showing that it is a downstream effect mediated by other factors, such as connective tissue growth factor (CTGF) that promotes collagen I synthesis (Hong et al. 2006). Collagen I is known to positively regulate retinal endothelial cell angiogenic properties and seems to mediate hypoxia-induced retinopathy in zebrafish through α_2 integrin (Liu et al. 2022).

In contrast to a positive effect of hypoxia on collagen synthesis, there are numerous studies in other types of cells that show a negative regulation of collagen I by hypoxia. Rabbit aortic smooth muscle cells under hypoxia produce less collagen, despite the increased synthesis of GAGs and hyaluronic acid (Pietilä and Jaakkola 1984). In human articular chondrocytes, HIF1α reduces *Col1a1* gene transcription through the transcription factor Sp3 (Duval et al. 2016), verified by the decreased collagen synthesis observed in mouse growth plate chondrocytes (Stegen et al. 2019). In porcine aortic endothelial cells, hypoxia has been shown to cause a significant decrease in collagen synthesis (Levene et al. 1982) and to induce endothelial-to-mesenchymal transition as inferred by the increased expression of vimentin and α-smooth muscle actin and the decreased expression of VE-cadherin and CD31 (Liu et al. 2019).

Collagen XV has been recently shown to be positively regulated by hypoxia through HIF1α in human mesenchymal stromal cells and may be implicated in their osteogenic potential (Lambertini et al. 2018). In kidney cells, hypoxia suppresses collagen IV α_2 expression through HIF1α (Sanaei-Ardekani et al. 2021). In both cases, it is unclear whether such effects occur in endothelial cells and/or if they may have an impact on angiogenesis.

8.2.2 Hypoxia Effect on Intracellular Collagen-Modifying Enzymes

Collagen mRNA is translated to procollagen that undergoes post-translational modifications within the endoplasmic reticulum (ER). Collagen proline hydroxylation is mediated by prolyl 4-hydroxylase α-subunit (P4HA). Three isoforms of P4HA have been identified, namely P4HA1, P4HA2, and P4HA3. All α-subunit isoforms form A2B2 tetramers with the prolyl 4-hydroxylase β-subunit (P4HB) and generate the P4H1, P4H2, and P4H3 holoenzymes, respectively. P4Hs modify proline to 4-hydroxyproline, and this step is essential for the thermal stability of the collagen triple helix (Rappu et al. 2019). Non-prolyl hydroxylated procollagen α-chains are

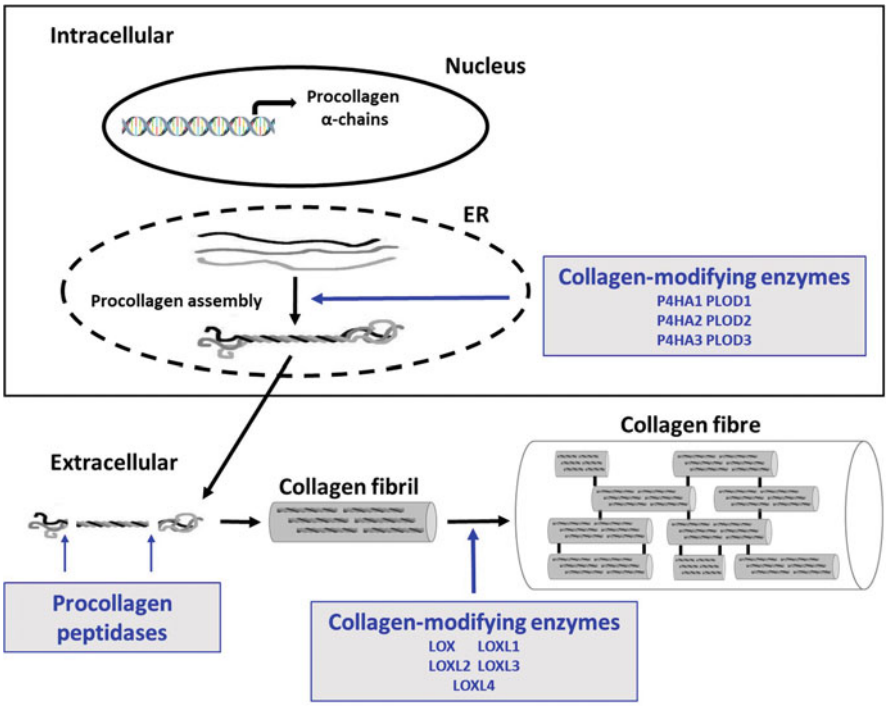

Fig. 8.2 Biosynthesis of fibrillar collagens. The intracellular steps involve the synthesis of procollagen polypeptides and the modification of these molecules in the ER and the Golgi apparatus by P4HA and PLOD enzymes. In the extracellular space, the non-helical termini are cleaved, and the mature collagen proteins form a collagen fibril. Collagen fibre formation is initiated by collagen crosslinking, catalysed by LOX family members

improperly folded and degraded, leading to decreased collagen deposition (Yamauchi and Sricholpech 2012). Collagen lysine hydroxylation is mediated by the three procollagen-lysine 2-oxyglutarate 5-dioxygenase (PLOD1, PLOD2, and PLOD3) enzymes. Hydroxylated lysine residues contribute to increased stability of the collagen cross-links, leading to increased tissue stiffness (van der Slot et al. 2004) (Fig. 8.2).

Hypoxia increases the expression of P4HA1, P4HA2, PLOD1, and/or PLOD2 in many cell types, e.g., fibroblasts (Gilkes et al. 2013; Rosell-García et al. 2019; Morimoto et al. 2021), chondrocytes (Grimmer et al. 2006), cytotrophoblasts (Highet et al. 2015), human gingival fibroblasts and human periodontal ligament cells (Morimoto et al. 2021), hepatic stellate cells (Copple et al. 2011), sarcoma cells (Eisinger-Mathason et al. 2013), and endothelial cells (Becker et al. 2021 and Table 8.1). This may lead to an increased hydroxylation of collagen and stabilization and stiffening of the collagen matrix. Abrogating the expression of HIF1α or P4HA1 and P4HA2 has been shown to reduce collagen deposition from fibroblasts in vitro (Gilkes et al. 2013). Similarly, a HIF1 pathway inhibitor has been shown to inhibit

Table 8.1 Expression of collagens and collagen-modifying genes in hypoxia-cultured human microvascular endothelial cells

Gene	N-fold average	St dev	*t*-test	Mean expression
COL1A2	5.60	3.55	0.05	2.26
COL4A1	1.23	0.16	0.05	457.84
COL27A1	1.31	0.12	0.00	18.46
FKBP14	0.71	0.15	0.03	13.61
LAMA3	0.59	0.14	0.01	3.15
LAMB2	1.14	0.09	0.01	98.20
LOXL2	1.45	0.25	0.01	264.35
P4HA1	2.08	0.34	0.00	57.73
P4HA2	1.32	0.06	0.00	91.02
PLOD1	1.51	0.36	0.01	183.68
PLOD2	1.92	0.36	0.00	175.94
PLOD3	1.30	0.08	0.00	90.13
SLC39A13	1.09	0.07	0.04	59.65

Remark by Pieter Koolwijk

hypoxia-induced P4HA1 and P4HA2, decrease prolyl hydroxylation, and induce proteolytic cleavage of collagen VI, which is the main collagen produced in uveal melanoma, thus inhibiting uveal melanoma cell invasion (Kaluz et al. 2021). Hypoxia can also up-regulate P4H1 at the level of translation, independently of HIF1α, as has been shown in human fibroblasts (Fähling et al. 2006). It has been also suggested that HIF1α but not HIF2α mediates the stimulatory effect of hypoxia on P4H enzymes (Aro et al. 2012; Bentovim et al. 2012).

Collagen hydroxylation by P4H enzymes has been shown to regulate angiogenesis. Compounds that inhibit proline hydroxylation and maturation of collagen in endothelial cells have been shown to inhibit angiogenesis in vitro (Clement et al. 2002). In the same line, up-regulation of P4HA2 by p53 results in inhibition of angiogenesis (Teodoro et al. 2006). On the other hand, such inhibitors have been shown to enhance angiogenesis (Warnecke et al. 2003; Zhu et al. 2019) but the stimulatory effects seem to be attributed to non-collagen related effects of such inhibitors that may also inhibit the HIF PHDs or to a direct effect of P4H enzymes on HIF-α stability (Xiong et al. 2018).

Five different human microvascular endothelial cell isolations were cultured for 14 days at normoxic (20% of oxygen) or hypoxic (1% of oxygen) conditions and genome-wide sequencing was performed on a Illumina platform. For details, see Nauta et al. (2016, 2017).

8.2.3 Hypoxia Effect on Extracellular Collagen-Modifying Enzymes

Once secreted extracellularly and following cleavage of the two non-helical termini by proteinases, fibrillogenesis is initiated. During this process, specific lysine and hydroxylysine residues in the N- and C-telopeptides are oxidatively deaminated by lysyl oxidase (LOX), a step necessary for the formation of covalent intra- and intermolecular cross-links (Yamauchi and Sricholpech 2012) (Fig. 8.2).

The expression of LOXs is induced by hypoxia in tumour cells (Wang et al. 2018; Calvo-Anguiano et al. 2018), in fibroblasts (van Vlimmeren et al. 2010), in adipocytes (Anvari and Bellas 2021), and in endothelial cells (Guadall et al. 2011; Becker et al. 2021; Table 8.1). LOX-cross linked collagen activates endothelial cells in vitro and angiogenesis in vivo and correlates with the number of blood vessels in colorectal and breast cancer (Baker et al. 2013), in oral squamous cell carcinoma (Shih et al. 2013), and in hepatocellular carcinoma (Yang et al. 2019). LOX expression has been found higher in tumour endothelial cells compared to normal endothelial cells and to regulate endothelial cell migration and tube formation (Osawa et al. 2013; Shi et al. 2018). In favour of a positive effect of LOX in the regulation of angiogenesis, it has been shown that in synovial membranes, the expression of LOX positively associates with the microvascular density (Wang et al. 2017). More recently, it was shown that an interplay between LOXs and VEGFA/TGFβ is essential for the maturation of blood vessels (Grunwald et al. 2021). Lysyl oxidase-like protein-2 (LOXL2) in endothelial cells has also been identified as a hypoxia target that is involved in the regulation of angiogenesis (Bignon et al. 2011) through its effect on collagen IV scaffolding in the BM of new blood vessels (Bignon et al. 2011), but also on the deposition of other ECM components, such as fibronectin (Umana-Diaz et al. 2020). It has been shown that LOXL2 modulates endothelial-to-mesenchymal transition and thus activates angiogenic functions of endothelial cells (de Jong et al. 2019), a mechanism that has also been described for hypoxia (Liu et al. 2019). It is also of interest that LOXL2 has been found on the exterior of endothelial cell-derived exosomes and is significantly up-regulated in exosomes derived from hypoxic endothelial cells (de Jong et al. 2016). Finally, LOXL2 has been shown to stabilize HIF1α from PHD-dependent hydroxylation, supporting the existence of a positive feedback loop that enhances the effects of hypoxia (Li et al. 2021).

8.2.4 Hypoxia Effect on ECM Remodelling Enzymes

Proteolytic cleavage of the ECM is part of its remodelling and is important for regulating its composition and structure, as well as for releasing biologically active molecules. During angiogenesis, endothelial cells produce numerous enzymes that cleave ECM proteins to support various critical steps of the process: (a) BM

breakdown at the initiation of angiogenesis to favour endothelial cell mobility; (b) invasion into collagen I or fibrin matrices; and (c) new lumen formation. Besides degradation of endothelial BM to allow for endothelial cell migration and new lumen formation, proteases also liberate and/or modify pro- and anti-angiogenic factors that are stored in the ECM, contribute to ectodomain shedding of growth factor receptors that are thus activated, cleave and liberate cytokines from membrane-bound precursors, and generate ECM protein fragments that inhibit or activate angiogenesis (Davis et al. 2002; Gonias et al. 2000; Selvarajan et al. 2001; Davis and Bayless 2003; van Hinsbergh and Koolwijk 2008).

MMPs are a major group of enzymes involved in ECM degradation. They are produced either as soluble or as cell membrane-anchored proteinases and have wide substrate specificities towards many ECM proteins (Laronha and Caldeira 2020). Hypoxia has been shown to increase the expression and activity of both MMP2 and MMP9 in pulmonary arterial endothelial cells in vitro and pulmonary artery endothelium in vivo (Liu et al. 2018). Hypoxia has been also shown to stimulate MMP9 expression in brain endothelial cells but not pericytes (Boroujerdi et al. 2015). MMP9 has been implicated in the hypoxia-induced blood–brain barrier disruption and its inhibition has been suggested as a potential basis for therapeutic strategies to treat brain oedema (Bauer et al. 2010). Interestingly, MMP9 seems to not be essential for hypoxic-induced cerebral angiogenesis, but it affects the post-hypoxic vascular pruning following degradation of laminin and claudin-5 (Boroujerdi et al. 2015). Hypoxic pre-treatment of bone marrow mesenchymal stem cells has led to enhanced MMP9 expression levels, among others, and after being transplanted into rats with diabetic lower limb ischaemia, these cells significantly improved angiogenesis (Liu et al. 2015). In monkey choroid-retinal endothelial cells, hypoxia has been shown to primarily induce MMP2 activity (Ottino et al. 2004) and enhancement of MMP2 by hypoxia in endothelial cells has been linked to their enhanced migration and apoptosis but not tube formation; at the same time, hypoxia decreased membrane type 1 MMP (MT1-MMP) and tissue inhibitor of MMP 2 (TIMP2) mRNA and protein levels, suggesting an MT1-MMP-independent MMP2 activation (Ben-Yosef et al. 2005). The decrease of MT1-MMP and TIMP2 by hypoxia has been observed in both short (6 h) and prolong (24 h) hypoxia, while MMP2 has been found up-regulated only at prolonged hypoxia (Ben-Yosef et al. 2002). As has been shown for collagen, the effect of hypoxia on MMPs may be mediated by CTGF that increases the expression of MMPs and decreases the expression of TIMPs by vascular endothelial cells (Kondo et al. 2002). The effect of hypoxia on MMP2 expression and neovascularization in retinas exposed to hypoxia has also been shown to be mediated by ANGPT2 (Feng et al. 2009).

Besides a direct effect of hypoxia on MMPs in endothelial cells, hypoxia can also regulate MMP expression and activity in other cells that subsequently affect tissue angiogenesis. For example, hypoxia in rheumatoid arthritis fibroblasts has been shown to up-regulate MMPs 2, 8, and 9, as well as MT1-MMP, but to have no effect on TIMPs 1 and 2 and to decrease MMP13. Conditioned medium of these cells stimulated angiogenesis in vitro (Akhavani et al. 2009). In human intervertebral disc cells, hypoxia has been shown to significantly increase MMPs 1 and 3 and decrease

TIMPs 1 and 2, thus enhancing the angiogenic ability of intervertebral disc cells during inflammatory reactions in vitro (Kwon et al. 2017). In human cancer cells, MT4-MMP has been shown to be up-regulated by hypoxia or overexpression of HIF1α through activation of the transcription factor SLUG (Huang et al. 2009), and such up-regulation has been linked to invasiveness, metastasis, and angiogenesis (Huang et al. 2009; Host et al. 2012). In glioblastoma cell lines, hypoxia has been shown to significantly enhance MMPs 2 and 9, as well as collagen I. Interestingly, expression levels of angiostatins, MMP-dependent proteolytic products of plasminogen/plasmin, were also increased by hypoxia, despite the pro-angiogenic phenotype of these cells (Emara and Allalunis-Turner 2014). On the other hand, plasma levels of MMP2 and angiostatin, but not plasminogen/plasmin or MMP9, were found significantly decreased in a swine model of neonatal hypoxia compared to the normoxic group (Emara et al. 2007). Angiostatin has been shown to decrease MMP2 expression in human microvascular endothelial cells exposed to hypoxia, thus inhibiting endothelial cell migration (Radziwon-Balicka et al. 2013). Besides angiostatin, the anti-angiogenic cleavage product of collagen XVIII, endostatin, has been also found increased in extracts from tissues exposed to hypoxia and the elevated amounts of endostatin within the aortic wall of mice exposed to hypobaric hypoxia might contribute to the hypoxia-induced development of pulmonary hypertension due to decreased angiogenesis (Paddenberg et al. 2006).

Another enzyme family that is important in ECM remodelling is that of the serine proteases. The plasminogen activators, urokinase-type (uPA) and tissue-type (tPA), target plasminogen to generate plasmin, an enzyme that degrades many ECM proteins e.g., fibrin, fibronectin, and laminin (Engelse et al. 2004). The uPAR on many cells, including endothelial cells, not only binds uPA and thereby localizes its activity, but can also activate intracellular signalling pathways to coordinate ECM proteolysis (Fig. 8.3). Since uPAR lacks transmembrane and intracellular domains, transmembrane co-receptors, such as integrins, are required for its signalling (Smith and Marshall 2010).

Hypoxia through HIF1α has been shown to up-regulate the expression of both uPA and u-PAR in cancer cells, thus enhancing the proteolytic activity at the invasive front (Krishnamachary et al. 2003; Sullivan and Graham 2007) and promoting the epithelial-to-mesenchymal transition (Gupta et al. 2011), thus favouring invasiveness and metastasis. uPAR expression is also enhanced by hypoxia in endothelial cells and has been linked to enhanced angiogenesis in vitro (Graham et al. 1998; Kroon et al. 2000; Kroon et al. 2001; Choi et al. 2008). Hypoxia has been also shown to increase tPA and plasmin in human retinal microvascular endothelial cells (Valapala et al. 2011) through HIF1α (Huang et al. 2011). PAI1 mRNA and protein levels are also enhanced by hypoxia in bovine aortic endothelial cells (Uchiyama et al. 2000). On the other hand, prolonged hypoxia has decreased the production of uPA without affecting PAI1 (Nauta et al. 2016).

Besides the above-mentioned main families of proteolytic enzymes, several other proteases that play roles during the modulation of the matrix may be affected by hypoxia. For example, hypoxia stimulates the pro-angiogenic heparanase secretion in human retinal microvascular endothelial cells (Hu et al. 2012). Heparanase

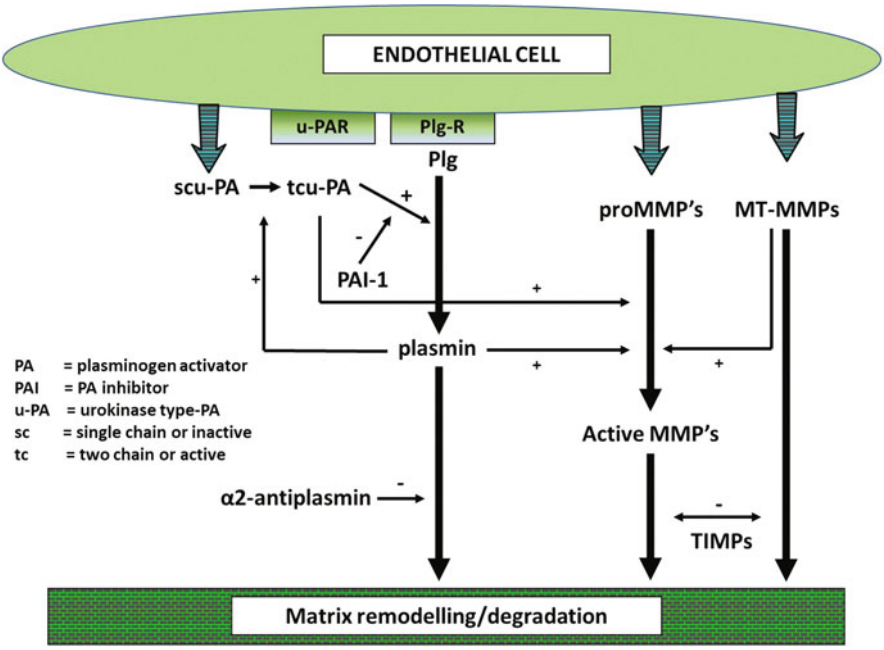

Fig. 8.3 The uPAR is an important regulator of ECM proteolysis. uPAR regulates the activity of the plasminogen activation system, an extracellular proteolytic cascade, by binding the serine protease uPA and its zymogen form, scu-PA. Plasminogen-derived plasmin cleaves and activates MMPs. Both plasmin and MMPs degrade many ECM components leading to proteolytic fragments with pro- or anti-angiogenic activities and activate or liberate growth factors that are sequestered in the ECM

specifically cleaves cell surface and ECM heparan sulphates at intra-chain sites and its mRNA levels have been correlated with enhanced angiogenesis in the adult rat hippocampus following repeated hypoxia exposures (Navarro et al. 2008). Some members of the ADAM (a disintegrin and metalloproteinase) protein family have also been shown to be up-regulated by hypoxia in other than endothelial cells. Examples include increased expression of ADAM17 following hypoxia treatment of various cancer cell lines (Rzymski et al. 2012). ADAM17 seems to be involved in hypoxia-induced CTGF expression in human lung fibroblasts and may thus play a crucial role in the development of lung fibrosis (Chen et al. 2017). In human glioblastoma specimens, HIF1α expression has been found strongly correlated with endothelial cell markers and ADAM10 expression, implying a potential effect of hypoxia on ADAM10 expression (Musumeci et al. 2015). Hypoxia also enhances ADAM8 expression and activation in human pancreatic cells (Gao et al. 2019).

8.2.5 *Hypoxia Effect on Integrins*

Integrins on endothelial cells serve as receptors for various ECM molecules, including collagens or collagen fragments, and regulate angiogenesis. Hypoxia has been shown to enhance expression of $\alpha_v\beta_3$ but not $\alpha_v\beta_5$ integrin in human umbilical vein endothelial cells (Walton et al. 2000; Ben-Yosef et al. 2005). In human microvascular endothelial cells, hypoxia enhances expression of α_v, β_1, β_3, and β_5 but not α_5 integrins (Befani and Liakos 2017). Hypoxia also increases $\alpha_v\beta_3$ integrin expression in other types of cells, such as melanoma cells (Cowden Dahl et al. 2005) and in myocardium early after infarction (Kalinowski et al. 2008). In human glioblastoma cells, hypoxia recruits $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins to the cell membrane, required for the activation of HIF1α through focal adhesion kinase and for angiogenesis stimulation (Skuli et al. 2009). In the developing mouse central nervous system, hypoxia enhances expression of both fibronectin and its receptor $\alpha_5\beta_1$ integrin localized on brain capillaries (Milner et al. 2008) and this has been correlated with brain endothelial cell proliferation (Li et al. 2012) or spinal cord vessel formation (Halder et al. 2018b) in response to hypoxia. On the other hand, HIF1α has been shown to decrease α_5 integrin subunit expression in human gastric cancer cells, thus regulating anoikis and metastasis (Rohwer et al. 2008). Chronic mild hypoxia in the central nervous system enhances vascular integrity by increasing the expression of laminins 111 and 411 and the laminin receptor $\alpha_6\beta_1$ integrin on endothelial cells, without affecting $\alpha_1\beta_1$ integrin (Halder et al. 2018a).

8.3 Summary and Future Perspectives

The ECM is important for diverse physiological and pathological processes and is altered in many disease states and following hypoxia. As summarized above, hypoxia enhances ECM stiffness to facilitate endothelial cell proliferation and migration; however, a hypoxia-induced increase of ECM stiffness above a certain level inhibits the formation of new blood vessels and induces fibrosis. Similarly, hypoxia affects the expression and activation of various proteases to remodel ECM, but the physiological consequences of such effects depend on the microenvironment of cells/tissues and the final balance between the pro- and anti-angiogenic molecules produced.

One concern in the interpretation of the data related to the effect of hypoxia on the ECM is the inherent complexity related to the variations in the duration and levels of hypoxia and its categorization as acute or chronic in all the in vitro and in vivo experimental models. It has been shown that in various in vitro studies, acute hypoxia lasts between 0.5 and 72 h, while chronic hypoxia between 4 h to several weeks (Bayer and Vaupel 2012) and it remains unclear whether and how any of such settings resemble pathologies in vivo. Besides chronic and acute, cycling hypoxia (also called intermittent hypoxia) is of interest since it also appears in tumours and

needs to be mimicked in vitro and in vivo (Saxena and Jolly 2019). In all cases, a strategy to control the effects of hypoxia would be the regulation of the expression and activity of HIFs, thus affecting ECM remodelling and angiogenesis (Gilkes et al. 2014; LaGory and Giaccia 2016; Lee et al. 2022).

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