

An update on angiogenesis modulators with a potential therapeutic role

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Abstract

Angiogenesis or formation of new blood vessels as a consequence of "sprouting" in a pre-existent vascular network represents a phenomenon of paramount importance in physiology and pathology. Although the molecular pathways and factors which modulate angiogenesis are similar regardless the clinical context, there are numerous aspects related to this process which are incompletely understood. At the present time, significant research focuses in finding the best method to control the pro-angiogenic factors as well as anti-angiogenesis since therapy of various medical conditions requires either stimulation or inhibition of formation of new blood vessels. However, angiogenesis is different in various vascular systems and organs. In this review, we will present the most promising factors that interfere with angiogenesis suggesting new or improved therapeutic methods in various pathological settings.

Keywords

SDF1 — HIF1 — MMPTie-2 — Notch — WNT — CCNA1 — PTEN — AGEs/RAGEs — HMGB1

Introduction

Blood vessels are formed during gastrulation stage by fibroblast growth factor (FGF) which acts upon the mesoderm to create accumulations of hematopoietic cells and angioblasts called "blood islands of the yolk sac". The angioblasts are in fact primitive endothelial cells. However, vascular endothelial growth factor (VEGF) promotes further differentiation of primitive vascular tubules from these angioblasts [1]. At this stage, the vascular structures are immature and friable but additional fibroblast growth factor (FGF)-dependent synthesis of vascular endothelial growth factor (VEGF) and its receptor would subsequently drive the formation of mature blood vessels [2]. This step is characterized by the acquisition of a mural cell coat which offers functional stability for the immature embryonic vessels and concludes the process of angiogenesis [3, 4]. In several pathological settings, including

in those associated with ischemia, angiogenesis requires the mobilization of bone marrow-precursor cells and their differentiation into circulating endothelial precursor cells. In ischemic lesions, it is described a direct attachment of these endothelial precursor cells to form the endothelium of capillaries located in the ischemic areas. Subsequently, this leads to the revascularization of affected tissues [5]. From a mechanistic perspective, regardless the clinical setting angiogenesis represents a multi-step process which begins with dilatation of pre-existing vessels and a vascular endothelial growth factor (VEGF)-dependent activation of endothelial cells. The next step consists of synchronous metalloproteinase-dependent capillary basement membrane disassembly and breakage of inter-cellular endothelial bunches mediated by a plasminogen activator. This results in a significant increased vascular permeability. In parallel, additional

degradation of peri-capillary matrix components, modulated by the same pro-angiogenic factors acts in concert with migration and proliferation of endothelial cells to create endothelial sprouts. Further organization of these sprouts leads to the formation of a network of endothelial cords. Depending on the interaction between various pro-angiogenic factors the ultimate result will be represented by vascular remodelling of this network with the formation of vascular tubular structures. Maturation of these young vessels involves

recruitment and proliferation of pericytes and formation of a new basement membrane and some smooth muscle fibres layer. Meantime, other factors such as transforming growth factor beta (TGF- β) can initiate differentiation of microvascular endothelial cells and pericytes into matrix-depositing myofibroblasts. Finally, after fusion of the newly formed vessels, they become functional and blood-flow is initiated through the vascular network [6, 7, 8] (Figure 1).

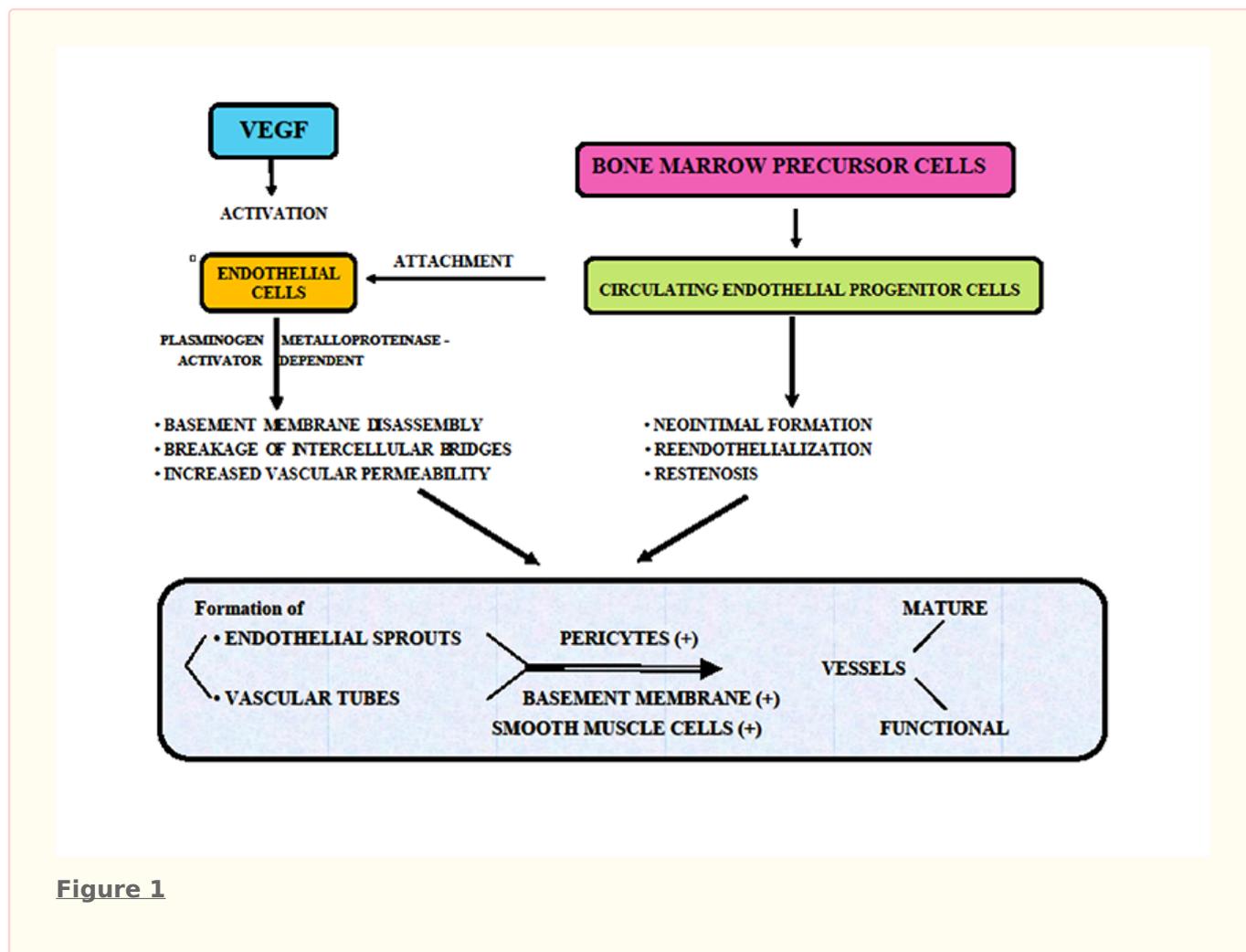


Figure 1

Figure 1 caption

Angiogenesis: VEGF and main factors

However, despite all of these, the process of angiogenesis is not completely understood. Meantime, current therapy of cancer or diabetes requires new improved anti-angiogenic pharmacological agents while in other pathological entities such as stroke an efficient manipulation of angiogenesis is yet to be implemented in a clinical setting. In this current article, we will present the most promising factors which interfere with angiogenesis in various clinical settings.

a. Stromal Cell-derived Factor 1 (SDF1)

Research studies investigating the angiogenic modulator role of Stromal Cell-derived Factor 1 (SDF1) have been conducted for quite some time but unfortunately, its complex actions are still incompletely understood. Initially, Mirshahi et al. (2000) have shown in an experimental study that Stromal Cell-derived Factor 1 (SDF1) acts upon C-X-C chemokine receptor 4 (CXCR4) and C-X-C Motif

Chemokine Ligand 12 (CXCL12) and has a significant pro-angiogenic effect in various experimental models [9]. The authors have shown that this factor is pro-angiogenic in vitro in a tridimensional fibrin gel promoting VEGF synthesis by endothelial cells. Also, SDF-1 has a pro-angiogenic effect in vivo in a model of rabbit corneal pocket [9]. In patients with glioblastoma multiforme, SDF-1/CXCL12 expression increases with increasing grade of the tumour and is better identified in more vascularized areas of the tumour [10]. It seems that the pro-angiogenic action of SDF-1 is enhanced by heme-oxygenase 1 (HO-1) which is locally manufactured by endothelial cells via protein kinase C zeta-dependent activation. Animal studies revealed that HO-1 deficient animals present with abnormal healing of the retinal blood vessels after SDF-1 administration compared with those subjects with HO-1 normal profile suggesting that HO-1 may act as a co-factor in this pathway [11].

Remarkably, SDF-1 is chemotactic and chemoattractant for a selected group of bone marrow cells bearing the C-X-C chemokine receptor 4 (CXCR4) which might be involved in tumour development as well as revascularization after ischemia. However, the actual mechanism of angiogenesis mediated by the interaction between SDF-1 and CXCR4 positive bone marrow cells is yet poorly understood. In experimental models of ischemia, apart from the mobilization of CXCR4 positive bone marrow cells, bone marrow cells that express VEGF receptors are also activated by SDF-1 [12]. Experiments conducted in patients with critical leg ischemia have shown that SDF-1 presents with two spliced forms alpha and beta. However, it seems that the beta variant has a more potent pro-angiogenic effect but both forms activate PI3K/Akt and p44/42 kinase [13].

In another pathological setting, SDF-1 partially counteracts the anti-angiogenic action of LDL. However, LDL decreases CXCR4 receptors on the surface of endothelial cells but SDF-1 administered in parallel with VEGF in Matrigel-based tube

formation assays-HUVECs, induces a full restoration of angiogenesis as well as a sustained anti-oxidative effect of endothelial cells suggesting that other molecular pathways might be involved [14].

Recent studies have also shown that in vitro SDF-1 promotes angiogenesis via activation of CXCR7 in a dose-dependent manner. Moreover, this mechanism stimulates the formation of tubules in HUVECs and in vivo systems. Remarkable, SDF-1/CXCL12 complex has a unidirectional chemoattractant action in HUVECs. It seems that CXCR7 action is facilitated by the PI3K/Akt phosphorylation pathway suggesting that SDF-1/CXCR7 represents a complex receptor for Akt-induced angiogenesis [15].

In vitro studies conducted in endothelial cells by Ziegler and Hughes (2014) indicate that SDF-1/CXCL12 complex activates mTOR while inhibition of CXCR4 and mTOR inhibits in vitro 3D angiogenesis [16]. Therefore, SDF-1 could be a co-factor which acts in concert with other mediators upon the same types of receptors. Studies conducted in rats with experimental carotid artery and intracranial aneurysms have indicated that SDF-1 administration is associated not only with a pro-angiogenic effect but also with a deleterious inflammatory reaction in the walls of both types of aneurysms which may lead to subsequent rupture [17]. However, other groups have reported that SDF-1 alpha overexpression in bone marrow-derived stromal cells promotes healing in osteonecrosis of the femoral head as well as angiogenesis [18].

b. Hypoxia-inducible factors (HIF)

Hypoxia is responsible for the onset of angiogenesis, through releasing of the pro-angiogenic hypoxia-inducible transcription factors HIF1 and HIF2. Particularly, HIF1 induces trans-activation of gene-promoting angiogenesis and post-transcriptional stabilization of VEGF mRNA, followed by up-regulation of VEGF and other pro-angiogenic substances [20, 21, 22] (Figure 2).

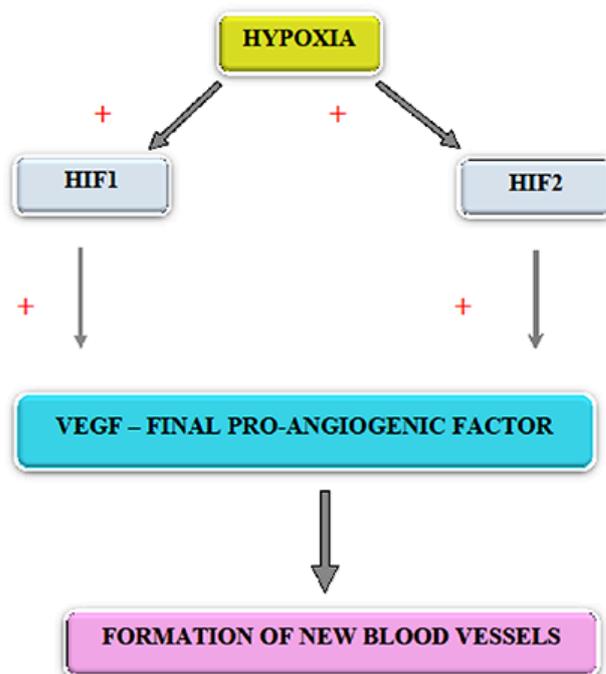


Figure 2

Figure 2 caption

Modulation of angiogenesis by hypoxia

At the level of the central nervous system, it seems that the most important mechanism modulating the extent of the vascular network is represented by an interplay between angiolysis and angiogenesis induced by HIFs acting in concert with VEGF as well as the Ang2/PGE2/COX2 complex [19]. However, previous studies have shown that HIF1 is activated in tissue hypoxia and is rapidly degraded during normal tissue oxygenation [20, 21, 22]. On the other hand, oxygen excess can inhibit the formation of new vessels and even their regression, similar to oxygen-induced retinopathy in premature infants [23].

Immunohistochemical studies have shown that in colorectal cancer lymphatic metastasis is correlated with a high level of HIF-1a [24]. Recently it has been reported that HIF-1a has a crucial role in starting on the chain of reactions that lead to carcinogenesis [25, 26]. This subunit, HIF-1a binds to CXCR4 which promotes angiogenesis as well as hematopoiesis and migration of malignant cells [27, 28, 29].

Recent research suggests that the pro-angiogenic activity of HIF-1a is enhanced by environmental toxins such as cadmium increasing significantly the risk of pulmonary adenocarcinoma [30]. Moreover, in-vitro studies conducted in prostate cancer cells indicate HIF1 controls transcription of miR-182 a factor which subsequently acts in concert with HIF to promote vascular development of prostatic cancer cells. It suggested that this synergic action of these two factors would result in an adaptation to hypoxic stress conditions during prostate cancer growth [31]. In oral squamous cell carcinoma, VEGF-A synthesis and subsequent cancer angiogenesis and development are enhanced by activation of the $\alpha\beta3$ /FAK/c-Src pathway which ultimately would stimulate the final molecular pathway represented by the EGFR/ERK/HIF1- α complex [32]. A detailed evaluation of tissue from smokers with a chronic obstructive pulmonary disease has suggested that an up-regulated HIF-1 may induce lung cancer in a K-ras mutant murine model [33]. All these data indicate that HIFs are a

potential therapeutic target.

Recently, based on the HIF structure several antagonists have been developed. Studies conducted in-vitro in human breast cancer cell line (MDA-MB-231) have revealed that analogues of the CJ-3k antagonist have an efficient anti-HIF activity suggesting that they might be effective as anti-cancer pharmacological agents [34]. Also, Qin RS et al. (2018) have successfully used metronomic therapy (low dose - high frequency) with Vinorelbine (NVB) administered with a known angiogenesis inhibitor, Endostar, to treat animal subjects with non-small cell lung cancer [35]. In the same study, they observed a significant decrease of HIF-1 as well as VEGF and CD31 associated with a decrease in tumour development as assessed by micro fluorine-18-deoxyglucose PET/computed tomography (18F-FDG PET/CT) [35]. However, the authors did not report a reduction in cancer-associated angiogenesis. This observation would suggest that while VEGF/HIF-1 are important for tumour growth the above mentioned metronomic therapy might have a direct anti-tumoral effect unrelated to the theoretical anti-angiogenic potential of the proposed therapy. Alternatively, one could speculate that the anti-tumoral effect is much more rapid than the anti-angiogenic effect of Vinorelbine combined with Endostar [35].

c. Matrix metalloproteinases (MMPs)

Angiogenesis requires degradation of the vascular basement membrane and extracellular matrix remodelling to allow endothelial cells to migrate and invade the surrounding tissues. Matrix metalloproteinases (MMPs) represent a group of several proteolytic enzymes which metabolize various extracellular matrix components including the basement membranes and the extracellular matrix facilitating migration of endothelial cells into surrounding regions [36].

Recent studies conducted in a murine model of ischemic stroke have reported that increased levels of matrix metalloproteinases-2 (MMP-2) are associated with post-stroke angiogenesis [37]. Increased levels of matrix metalloproteinases have been recorded in patients with traumatic brain injury. In this context, it seems that matrix metalloproteinases are responsible for blood-brain barrier disruption and leakiness [38]. Anyway, matrix metalloproteinases-2 (MMP-2) and matrix metalloproteinases-9 (MMP-9) promote retinal angiogenesis. However, inhibition of both factors by RNA interference (RNAi) stops the expansion of human retinal microvascular endothelial cells [39]. In addition, matrix metalloproteinases might also be involved in the process of diabetic wound healing. ND-36, an inhibitor of MMP-2 and MMP-9 administered in parallel with MMP 14 induces healing of chronic diabetic wounds by decreasing inflammation in association with stimulation of the angiogenesis process which in turn will promote wound epithelization. The same results have been recorded after administration of recombinant MMP8

[40].

However, matrix metalloproteinases-2 (MMP-2) and matrix metalloproteinases-9 (MMP-9) are inducing angiogenesis in cancer-promoting metastatic spread. In vitro studies performed on prostate cancer cell lines have shown that MMP9 overexpression is also associated with increased levels of murine double minute 2 (MDM2). The authors suggest that MDM2 might promote MMP9 driven angiogenesis [41]. Other experiments have indicated that the level of MMPs is modulated by $\alpha 2\beta 1$ integrin in breast cancer and endothelial cells [42]. Webb et al. (2017) have indicated that MMP9 and MMP2 promote the process of vascular metastasis and tumour growth in retinoblastoma, an ocular neoplasm described in children. This suggests that both MMPs are valid therapeutic targets in retinoblastoma patients [43]. Anyway, MMP-2 is associated with a low rate of survival in patients with colorectal cancer. Interestingly, MMPs may be inhibited by naturally occurring inhibitors. Allyl isothiocyanate (AITC) has been detected in a number of vegetables. Its action results in a decrease in the levels of MMP-2, MMP-9, and mitogen-activated protein kinases (MAPK) -p-JNK, p-38 and p-ERK [36]. Recent studies have indicated that matrix metalloproteinases-9 (MMP-9) is controlled by mitochondria-associated reactive oxygen species (mtROS). The mtROC activity is in turn stimulated by NADPH oxidase 4 (NOX 4) and overall cancer metastasis is promoted [44]. However, at the present time, new factors are tested for their anti-MMP action in cancer metastasis. In this context, eupatilin inhibits angiogenesis-mediated in human hepatocellular lines by decreasing the levels not only of MMP-2 but also VEGF and HIF-1 [45].

Also, MMP2 and MMP9 could be involved in the etiopathogenesis of preeclampsia. In a murine model of reduced uterine placental perfusion, it was discovered that the level of both these two factors is considerably reduced compared with normal subjects. Therefore, it was concluded that MMPs may be responsible for a significant reduction in uterine and placental vascularization [46].

Overall, these data would suggest that matrix metalloproteinases would have complex differential effects in various tissues, but at the present time, we do not have efficient pharmacological agents to modulate the activity of MMPs.

d. Angiopoietins/Tie-2

Recent studies suggest that angiopoietins are of paramount importance in normal angiogenesis [47]. This group includes several factors such as Ang-1, Ang-2, Ang-3 and Ang-4. Currently, it is known that Ang-1 which acts upon endothelial cells on Tie-2 which is a receptor tyrosine kinase promoting endothelial cells stabilization and their survival. Woolf et al. (2009) suggest that genetically Ang-1-deficient animals die as a result of vascular immaturity, while those subjects deficient in Ang-2 die very shortly after birth, displaying anomalies

of retinal vascularization as well as abnormal lymphatics. These results indicate that angiopoietins are crucial for vascular differentiation and maturation [48].

Subsequent to the activation of Tie-2, mesenchymal cells are recruited to induce pericyte attachment and ultimately the formation of "non-permeable" vessels. It was reported that Ang-2 in low doses inhibits the activation of Tie-2 but high concentrations of Ang-2 would promote the activation of Tie-2 [49]. Furthermore, Felcht et al. (2012) have confirmed that Ang-2 binds to Tie-2 and behaves as a negative modulator of Ang-1/Tie-2 binding [50]. Therefore, it is considered that Ang-2 is an Ang-1 antagonist which prevents pericyte attachment but induces angiogenesis in the presence of VEGF-A [51]. In patients with diabetic retinopathy, in concert with VEGF, Ang-2 and Tie-2 promote neovascular development while

breast hyperplasia is associated with an Ang-2 pro-angiogenic response [52, 53]. Further experiments conducted in a mice model of myocardial infarction have shown that myocardial ischemia promotes an increase of Ang-2 and Tie-2. However if Ang-1 level is higher than Ang-2 the size of the myocardial ischemic lesion is smaller than in cases in which Ang-2 is elevated over Ang-1 [54].

In healing wounds, Ang-1, Ang-2 and Tie-2 are identified at the level of myofibroblastic cells. Their level correlates positively with VEGF and new vessels formation [55]. In some cancers such as glioma, angiogenesis could be promoted subsequent to Ang-2 binding to alpha(v)beta(1) integrin on endothelial cells and activation of focal adhesion kinase signaling pathway (FAK) as well as an over-expression of matrix metalloproteinase 2 (MMP2) which is a pro-angiogenic factor [56] (Figure 3).

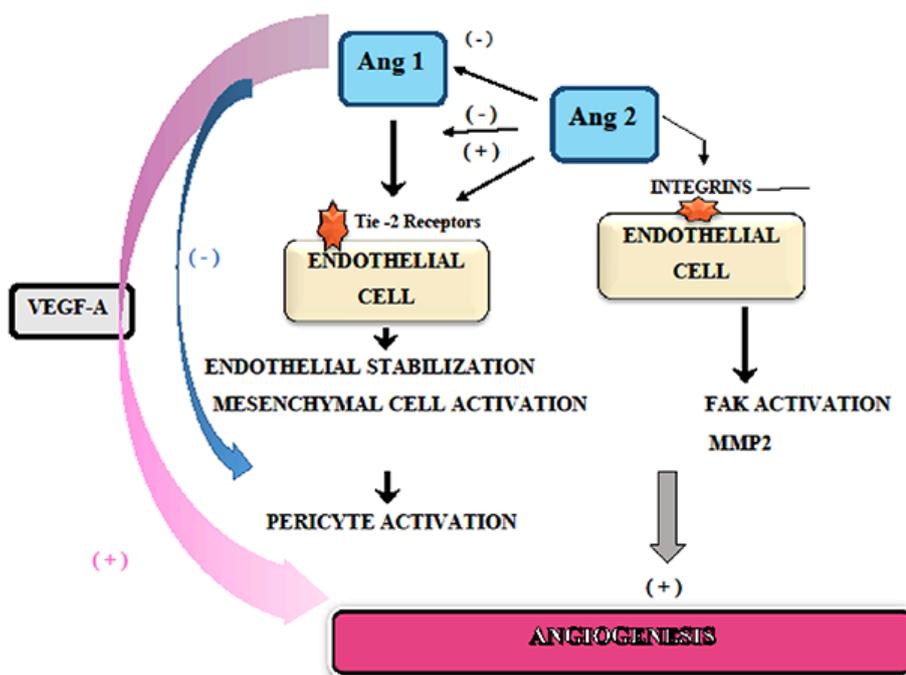


Figure 3

Figure 3 caption

Angiogenesis and Angiopoietins/Tie-2 system

The Ang-1 / Tie-2 interaction promote the development of metastases in cases of

neuroendocrine tumours of pancreas and stomach attracting in close proximity to a tumour a population of monocytic cells expressing Tie-2. It seems that these cells enhance both tumour-associated angiogenesis and regional inflammation [57]. However, recent in vitro research using mesothelioma cells over-expressing Ang-1 and Ang-2 transplanted in rats have revealed that low Ang-1 level is characteristic for the epithelioid mesothelioma type while tumours characterized by both high levels of Ang-1 and Ang-2 are associated with vascularized lesions [58].

Interestingly, factors targeting Ang-2 in parallel with VEGF such as ANG2 have been recently developed. ANG2 reduces vascularization in melanoma, pancreatic and breast cancer while inducing tumour necrosis via a CTL-dependent mechanism promoting perivascular deposition of CD8+ cytotoxic T lymphocytes (CTLs) which express interferon- γ (IFN γ) as well as programmed cell death ligand 1 (PD-L1) in a tumour's endothelial cells. This suggests that the anti-VEGF-a and anti-Ang2 action of ANG2 could be further enhanced by PD-1 inhibition [59].

e. Notch signalling

This molecular pathway modulates cellular development during embryonic development [60]. In animal models, a deficiency of Notch-1 determines an early embryonic death due to disruption of the angiogenesis process [61]. The Notch family of proteins includes Notch-1, Notch-2, Notch-3, and Notch-4 representing a group of transmembrane heterodynamic receptors that interact with the ligands located in the cell membranes: Jagged1, Jagged2, and delta-like ligands (Dll1, Dll3, and Dll4) [62]. It was suggested that Notch pathway functionality is modulated by factors such as multiple- post-synaptic density protein (MPDZ) by facilitating the interaction between DLL1/4 with Nectin-2 which is located at the adherens location. Inhibition of MPDZ activity is associated with Notch pathway inhibition and angiogenesis. However, the newly formed blood vessels are not functional [63].

Recent studies conducted in a transgenic murine model have revealed that endothelial Notch modulates the synthesis of local lipase as well as other factors such as Fabp4, Angptl4 and CD36 which may be regulating the transport of free fatty acids across the endothelium. It was shown that in mutant animals with non-functional Notch signalling there is a significant accumulation of lipids in plasma [64].

The Dll4/Notch-1 has a crucial role, modulating VEGF-dependent luteal angiogenesis [65]. Notch1 acts on Hey2 and HeyL and modulate myofibroblastic transformation of rat hepatic stellate cells. Also, Notch-1 is expressed by the synovial tissue enhancing VEGF/Ang-2 angiogenesis in inflammatory arthritis in response to hypoxia [66, 67, 68]. In addition, Notch-1 has a role of paramount importance in pulmonary hypertension,

modulating vascular remodelling [69]. Moreover, Notch signalling has a significant role in skeletal development, as well as bone remodelling. Mutations of Notch-2 are associated with Hajdu Cheney syndrome characterized by extensive osteoporosis and fractures. Histological evaluation in these cases has revealed osteopenia and an increased number of osteoclasts. Interestingly, all these abnormalities are corrected by administration of a γ -secretase inhibitor [70].

Recent research investigating the endothelial cells have proved in a mice model that Notch pathways and the process of angiogenesis induced by this pathway is modulated by the SDF-1-CXCR4 pathway and the VEGF-A [71]. Notch pathway is inhibited by DAPT, a γ -secretase inhibitor. This is followed by significant vascularization of endometriotic lesions in C57BL/6 mice. However, the DAPT is not associated with any morphological changes in the endometriotic lesions suggesting that other molecular factors/pathways are implicated in the etiopathogenesis of this lesion [72].

However, a recent clinical study has revealed that Notch3 and Jagged-1 are significantly increased in cases of pituitary adenomas but the actual modulation of a potential molecular chain of events is not yet fully elucidated [73]. Previously, Dufraine et al. (2008) have suggested that Notch ligands might be involved in tumour angiogenesis [74]. Interestingly, blocking Dll4 resulted in an increased vascular development associated with a significant reduction in proliferation of tumour cells which is not completely understood Jagged1 in contrast, was described as facilitating the proliferation of tumour endothelium [74]. On another perspective, recent research has indicated that arresting Dll4-Notch1/Notch 4 interaction in the setting of the ischemic retina is very useful as it induces new capillaries development [75].

All these data would suggest that Notch signalling could represent a therapeutic target in selected cases of chronic inflammatory conditions and cancer.

f. Wnt/b-Catenin

Reis et al. (2012, 2013) suggest that Wnt/b-catenin complex is important for organ differentiation, vascular remodelling and angiogenesis [76, 77]. This complex is also involved in bone and cartilage remodelling, inducing healing of the osseous tissue [78]. Wnt/b-catenin pathway modulates endometrial physiological function as well as carcinogenesis [79]. Recent studies conducted in rats fed with a high-fat diet have suggested the Wnt pathway promotes a sustained production of IL-6, TNF- α , DKK and VEGF which act in concert to stimulate angiogenesis and atheroma plaque [80].

The Wnt/b-catenin pathway has a crucial role in the formation of the blood-brain barrier and negative modulation of cerebral tumoral angiogenesis after inducing platelet-derived growth factor- β (PDGF-B). Interestingly, in the above-mentioned

setting, Notch-1 activates the cascade Wnt/ β -catenin-Dll4/Notch-1 inhibiting process of cancer associated angiogenesis [76, 77]. Recent reports indicate that angiogenesis and vascular differentiation may be modulated by the Wnt ligands, more specifically by the Wnt 7a-Wnt 7b complex composed of MMP inhibitor Reck and an adhesion factor, Gpr124. They modulate not only brain angiogenesis but also dorsal root ganglia neurogenesis [81]. Therefore, it is not surprising that in this context, β -catenin deletion in endothelial cells leads to developmental angiogenic defects in the central nervous system [82, 83, 84].

However, Wnt pathway seems to promote the process of cancer metastasis and development in other types of cancer. Abnormalities related to the Wnt/ β -catenin pathway have been described in cases of pancreatic cancer resistant to chemotherapy [85]. The Wnt-ligand is a secreted glycoprotein that binds to Frizzled receptors, which triggers a molecular "cascade" resulting in the displacement of the multifunctional kinase Glycogen Synthase Kinase (GSK)-3 β from the Adenomatous Polyposis Coli (APC)/Axin/GSK-3 β -complex. However, if Wnt is blocked, β -catenin is degraded by the APC/Axin/GSK-3 β -complex. Also, phosphorylation of β -catenin by CK1 and GSK-3 β leads to its degradation through the β -TrCP/SKP complex. This complex has been revealed to be very important in lung carcinogenesis [86]. In addition, Linke et al. (2017) have indicated that in cases of Hodgkin's lymphoma, Wnt activates malignant cell chemotaxis towards the blood vessels as well as the local process of angiogenesis [87].

Interestingly, the root of *Scutellaria baicalensis* Georgi contains a flavonoid named Wogonoside which in cases of breast cancer has a strong anti-angiogenic action by inhibiting the Wnt/ β -catenin pathway. In fact, Wogonoside increases the Axin/Glycogen Synthase Kinase (GSK)-3 β complex and induces phosphorylation of β -catenin subsequent to an intracellular decrease of Wnt3a [88]. In addition, Park et al. (2011) have identified a pigment epithelium-derived factor (PEDF) which would inhibit Wnt/ β -catenin [89]. All these data would indicate without doubt that the Wnt/ β -catenin

molecular pathway represents a potential therapeutic target of significant clinical importance.

g. Cyclin A1- CCNA1

Cyclin A1-CCNA1 represents a 60 kDa protein which acts as a cell-cycle modulator synergic with cyclin-dependent kinases (CDKs), activating complex enzymes [90]. It also acts during meiosis and during the progression of the cellular cycle from G1 to S in somatic cells [91]. Recent studies have reported that the activity of CCNA1 is dependent on S100A6, a calcium binding protein that activates the endothelial cell-cycle senescence and progression. A decrease in this factor induces a significant decrease in CCNA1 and abnormalities of cell-cycle progression [92]. Bauer et al. (2016) have reported that CCNA1 represents a valid target for heme oxygenase -1 (HO-1). Overall, this interaction promotes enhanced angiogenesis [93]. Various cancers related to epigenetic changes are characterized by increased levels of methylated CCNA1. Testicular embryonal carcinomas and teratomas present with the highest levels of this factor. A hyper-methylated precursor of CCNA1 is recovered in the urine of vesical bladder cancer patients [94, 95]. In addition, increased CCNA1 levels have been reported in head and neck squamous cell carcinomas, as well as in melanomas and hepatocellular carcinomas [96, 97]. More importantly, it seems that CCNA1 acts in concert with VEGF in breast, prostate and ovarian carcinogenesis. A high level of CCNA1 suggests an increased proliferative risk, while an increased VEGFR2 expression indicates an advanced stage of cancer [98]. In prostate cancer, CCNA1 promotes invasiveness by acting upon androgen receptors and modulating MMP and VEGF expression [99]. Normal breast tissue displays low levels of CCNA1 while breast cancer tissue reveals both an increase in CCNA1 and VEGF. Remarkably, CCNA1 binds estrogen receptors (ER) suggesting that breast cancer progression results from multiple synergic interactions between various molecular pathways including modulators of angiogenesis such as VEGF but also cell cycle factors such as CCNA1 [100] (Figure 4).

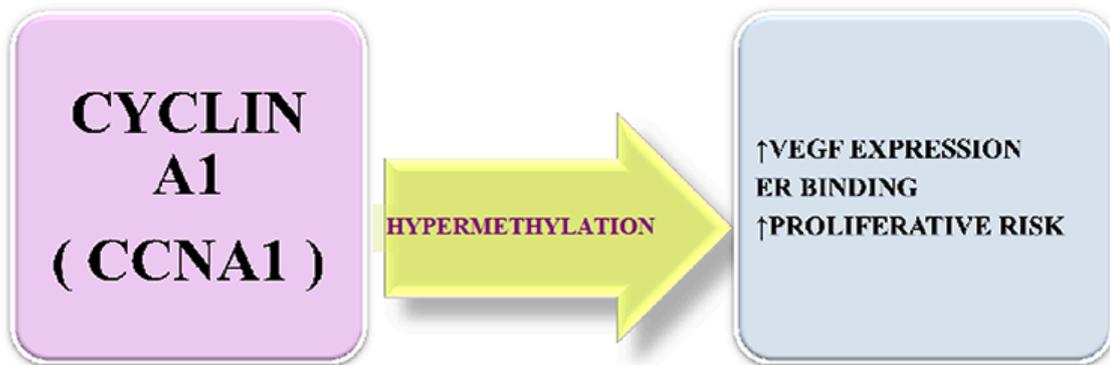


Figure 4

Figure 4 caption

Cyclin A1: mechanism of action

h. Follicle stimulating hormone (FSH)

Radu et al. (2010) have shown that FSH is present in the vascular network associated with a wide range of cancers such as breast, colon, pancreas, urinary bladder, kidney, lung, liver, stomach, testis and ovary. Also, FSH receptors have been identified in both benign and malignant tumours of adrenal gland [101, 102].

FSH receptors are also seen in metastases [103]. Until recently it was accepted that there are no FSH receptors in the normal tissues except in the ovarian and testicular parenchyma, more exactly in the granulosa and the Sertoli cell [104]. However, recent clinical studies have reported that FSH receptors are also located in the endothelial cells of the cervix, endometrium, myometrium including in the endometrial and cervical glands and myometrial muscle fibres. In addition, in pregnant women, FSH receptors are seen on the endothelial cells associated with umbilical cord and in both the fetal and maternal placenta. However, the role of

these receptors in these locations is not known [105].

Regarding the pro-angiogenic role of FSH, it was reported that binding to its receptor in the ovarian granulosa cells determines an up-surge of hypoxia-inducible factor 1 alpha (HIF-1 alpha), which subsequently determines an increase of vascular endothelial growth factor (VEGF) which is known to promote a rapid angiogenesis which has a significant role in further follicular development [106, 107]. Experimentally, it has been proven that FSH treatment during ovarian cryopreservation promotes ovarian survival by neo-angiogenesis subsequent to a sustained increase in VEGF/VEGFR2 [108]. In avian ovarian follicles, FSH induces a robust VEGF-A angiogenesis after prior induction of Annexin A2 (ANXA2) which is a calcium-dependent, phospholipid-binding protein [109]. Studies completed recently using ovarian epithelial cancer cells indicated that FSH increases the VEGF expression also via production of reactive oxygen

species (ROS) which in a second stage would turn on the Nrf2 pathway [110]. However, these findings have not been verified in a clinical setting but it is suggested that FSH exerts its positive effect on VEGF over-expression and associated angiogenesis by interacting with a variety of factors and molecular pathways. Overall, these data suggest that FSH could be a significant therapeutic target.

i. PTEN/PI3K-AKT complex

In general, PI3K-AKT induces angiogenesis while overproduction of PTEN inhibits angiogenesis in the chicken embryo [111]. It seems that stimulation of PI3K/AKT pathway and simultaneous suppression of PTEN has a beneficial effect protecting the heart from reperfusion injury [112].

PTEN (phosphatase and tensin homolog deleted on chromosome 10), an antagonist of PI3K-AKT, is a tumour suppressor, which is altered in several human cancers [113]. In addition, PTEN represents a target for miR-19a, a member of the microRNA clusters which modulates angiogenesis. Down-regulation of PTEN by miR-19a is followed by activation of AKT/GSK pathway and glycogen synthesis in hepatic cells [114]. Recent scientific reports suggest that in endothelial cells, PTEN is down-regulated by urokinase receptor (uPAR/CD87). Interestingly, PTEN down-regulation is associated with an increased density of newly formed blood vessels [115]. However, studies conducted in a PTEN deficient mouse model of prostate cancer have revealed that KLF5, a recently described transcriptional factor, induces cancer development subsequent to an increase in HIF1 α and inhibition of PI3K-AKT pathway [116].

The PI3K-AKT complex has a crucial role in modulating cell proliferation and growth as well as cellular survival initiated by other growth factors. Mice deficient in p110 α catalytic subunit of PI3K have more vascular defects including dilated cerebral vessels, anomalies endocardium development as well as a significant decrease in Tie-2 protein level. More importantly, in p110 α deficient mice, the vascular permeability induced by RAS and VEGF is significantly decreased. This suggests that PI3K has a crucial role in maintaining an adequate vascular permeability [117].

Some authors believe that PI3K is one of the most important molecular pathways implicated in carcinogenesis [118]. Erdreich-Epstein et al. (2016) have reported in a murine model of neuroblastoma that deletion of one allele of PTEN stimulates malignant development. This supports further assessment of factors targeting this pathway such as SF1126 as chemotherapeutic agents [119].

Remarkably, PI3K is sufficient by itself to induce angiogenesis partly by increasing the expression of HIF-1 and VEGF. A number of studies have demonstrated a modulation by PI3K of HIF-1 and VEGF expression in vascular endothelial cells, several types of neoplastic cells, smooth muscle cells, osteoblasts and mast cells

[120]. However, PI3K/AKT interacts with other molecular factors and pathways to promote angiogenesis. Immuno-histochemical studies conducted in patients with gastric cancer have indicated that PI3K/AKT is simultaneously activated with mTOR molecular pathway while the PTEN is downregulated [121].

j. B-Cell-specific Moloney Murine Leukemia Virus Integration Site 1 (Bmi-1)

B-cell-specific Moloney murine leukaemia virus Integration site1 (Bmi-1) represents a member of gene polycomb family. It was reported to have a significant etiopathogenic role in breast cancer, acute myeloid leukaemia as well as colorectal, and lung cancer, ovarian and nasopharyngeal tumours. In all these cancers, Bmi-1 promotes malignant cell proliferation and progression inhibiting apoptosis and cellular senescence [122, 123, 124].

Bmi-1 interacts with numerous molecular pathways implicated in cancer such as inhibition of p16/Rb and p19ARF/MDM2/p53 as well as Hedgehog pathway. It stabilizes the snail factor which is a transcription repressor which subsequently promotes epithelial-mesenchymal transition through modulation of PI3K/AKT/GSK-3 β [125, 126]. Bmi-1 promotes hepatic angiogenesis and modulates the NF- κ B/VEGF-C which is very important in cancer growth and development, particularly in gliomas. Other studies have suggested that aggressive gliomas are determined after activation by Bmi-1 of NF- κ B/MMP-9 molecular pathway [127, 128]. In head and neck squamous cell carcinomas, cisplatin administration promotes Bmi-1 synthesis and cancer stem cells formation. This could represent a potential mechanism of cancer resistance to cisplatin therapy [129]. These results would suggest that Bmi-1 could represent a potential therapeutic target in selected cases of cancer.

k. Galectins

Recent research suggests that Galectins are a group of pro-angiogenic molecules with a significant role in a multitude of pathological conditions including cancer and pre-eclampsia [130]. Therefore, numerous studies have been conducted to assess the potential of these molecules as therapeutic targets. In this context, Galectin-3 is a lectin which binds to β -galactosidase and displays three distinct structural domains: an NH₂-phosphorylation site, a collagen repeating part and a terminal COOH domain for binding carbohydrates. Galectin-3 has a role of paramount importance in embryonic growth and development, apoptosis, cellular differentiation and proliferation, and modulation of the immunological system. It is expressed by macrophages, eosinophils, and neutrophils and mastocytes. In addition, it is seen in gastrointestinal and respiratory epithelium, kidneys and sensory neurons [131].

Tissue remodelling after neural or heart ischemia is

characterized by increased expression of galectin-3 [132]. Recent research suggests that galectin-3 is a pro-angiogenic factor promoting the action of VEGF and b-FGF [133]. Dos Santos et al. (2017) have indicated that galectin-3 in concert with hypoxic conditions stimulates new blood vessel formation via activation of the JAG1/Notch-1 molecular pathway [134]. Also, Etulain et al. (2014) have demonstrated that Galectin-1, 3 and 8 exert their pro-angiogenic role via VEGF release from human platelets promoting in vitro tubular formation and endothelial cell proliferation [135].

Interestingly, migration of type M2 cancer macrophages is taking place according to a galectin-3 gradient and increased expression of this protein is correlated with malignant angiogenesis, tumour growth and aggressiveness [136]. Research conducted in a melanoma cell line has indicated that in transforming growth factor beta 1 (TGFβ1) activated macrophages, tumoral angiogenesis is impaired by inhibition of Galectin-3 pathway [137].

At the present time, galectin-3 explains progression in breast, prostate and pancreatic cancers, melanoma, follicular thyroid tumours and neuroblastoma [138, 139, 140, 141, 142, 143]. Also, in oral squamous cell carcinoma, galectin-3 in parallel with another lectin named galectin-1, promotes angiogenesis, cell proliferation and survival [144].

Park et al. (2015) have shown that in cultures of osteosarcoma cells, inhibition of galectin-3 is followed by down-regulation of VEGF, IL-8, IL-6, phospho-Stat3, MMP2/9 and MCP-1 as well as an inhibition of several molecular pathways such as Wnt/beta-catenin, FAK, ERK1/2, PI3K/AKT, Src and Lyn. All these are translated into a significant decrease in cell migration and invasiveness [145]. In Her-2 negative breast cancer cells, galectin-3 in concert with Annexin-A 2 modulates the epidermal growth factor receptor pathway which promotes cancer development [146]. In breast tumour development, hypoxia significantly increases production of galectin-3 which seems to be responsible for an aggressive phenotype while in concert with senescent cell-derived growth factors, galectin-3 induces colorectal cancer cells growth [147, 148].

I. Advanced Glycation End Products (AGEs)/ Receptors for Advanced Glycation End-products (RAGEs)

Hoffmann et al. (2002) have observed that in the eye, Advanced Glycation End Products (AGEs) not only that increase in newly formed blood vessels but also promote proliferation of Müller cells, retinal pigment epithelial cells, and choroidal endothelial cells [149]. AGEs are proteins or lipids modified by non-enzymatic glycation and oxidation processes. These appear in diabetic chronic hyperglycemia due to oxidative stress. AGEs act upon specific receptors named receptors for advanced glycation end products (RAGEs). These are seen in monocytes and macrophages, smooth muscle fibers, lymphocytes

and endothelial cells [150]. AGEs-RAGEs interaction, triggered by the activation of an inflammatory process potentiated by NF-kB stimulates the accumulation of extra-cellular matrix accelerating the formation of atherosclerotic plaques and cardiac fibrosis [151]. Recently published studies have revealed that suppression of RAGE improves the angiogenic response to ischemia. The authors explain the observed effect by a significant increase in VEGF [152]. Interestingly, this VEGF related mechanism has also been described in human synoviocytes [153]. Recent studies suggest that RAGEs could be involved in carcinogenesis by modulating the VEGFR2 and increasing vascularization in renal cell cancer patients. RAGEs also correlate with a reduced survival as well as decreased metastasis-free evolution. All these suggest that RAGEs could be a prognostic marker in patients with renal cell carcinoma [154]. Additional experimental studies have revealed that interaction AGEs-RAGEs in glioma-associated microglia promotes angiogenesis [153].

m. HMGB1

The HMGB1 protein acts upon several receptors TLR4 (Toll-like receptor 4), RAGE (receptors for advanced glycation end-products), CD24 and TIM-3 and modulates replication, transcription, recombination, and repair of DNA [155, 156]. In vitro studies have shown that HMGB1 promotes endothelial cell migration and sprouting of newly formed blood vessels in a dose-dependent manner [157]. HMGB1 initiates expression of Ang-2 and angiogenesis in skeletal muscle in response to tissue hypoxia [158]. HMGB1 interacts with RAGEs and stimulates the production of pro-angiogenic and pro-inflammatory factors [159].

Also, as results of its interaction with RAGEs, HMGB1 facilitates the pro-tumoral action of type 2 macrophage phenotype induced by IL4/IL-13, including angiogenesis [160]. After intra-cerebral haemorrhage, HMGB1 acts also upon RAGEs to promote angiogenesis via up-regulation of VEGF [161]. Studies performed in a murine model of rheumatoid arthritis have indicated HMGB1 would exert its pro-angiogenic effect in synovium via stimulation of HIF-1α. In this context, therapy with anti-HMGB1 antibody would prevent the development of new blood vessels as well as synovial inflammation while inducing a significant decrease in HIF-1α [162].

Interestingly, in the cancer setting, HMGB1 interacts with mitogen-activated protein kinase (MAPK)-NF-kB and mTOR molecular pathways but it seems that HMGB1 has a dual effect [155, 163]. On one side it stimulates cancer-associated angiogenesis while promoting the anti-neoplastic effects of T lymphocytes [164, 165, 166]. In acute myeloid leukaemia, HMGB1 promotes malignant development and progression via increased VEGF secretion which is dependent on the functionality of Tim-3 immune receptor [167].

n. Leptin

Leptin is a factor or an “adipokine” secreted by the adipose tissue which acts at the central nervous level to regulate satiety and appetite. It also interferes with endothelial dysfunction which is a risk factor for atherosclerosis [168]. Leptin levels correlate with adipose tissue size and body weight modulating bone physiology, immunological function and reproduction. More importantly, leptin induces the formation of new blood vessels [169]. Recent research suggests that leptin levels promote proliferation and differentiation of angiogenic endothelial cells in vitro and in vivo [170]. Leptin modulates the process of angiogenesis in skeletal muscles acting as a paracrine factor via platelet-derived growth factor receptor α (PDGFR α) and platelet-derived growth factor receptor β (PDGFR β) positive endothelial cells [171].

Also, leptin seems to have a significant role in the embryological development of the cardiovascular system. The hypoplastic left heart syndrome is characterized by leptin dysregulation. Since leptin has a pro-angiogenic effect, recent studies suggest that high levels of leptin recorded in subjects with hypoplastic left syndrome might be a natural attempt at correcting morphological abnormalities of the cardiovascular system [172]. Leptin promotes skin wound healing. Experimental studies conducted in a mouse model have indicated that topically administered leptin acts upon leptin receptor located in the skin to facilitate the differentiation and functionality of keratinocytes and local angiogenesis which would promote wound healing [173]. Moreover, leptin is capable of promoting expression in various tissues of a wide range of pro-angiogenic factors including the most powerful pro-angiogenic mediator, VEGF and its receptor VEGFR2. It also promotes the synthesis of IL1, Notch, MMPs, TIMP and integrins [174].

Leptin has been linked to the development of breast cancer [175]. Interestingly, the leptin receptor and estrogen receptor are co-expressed in breast cancer suggesting that leptin may play a significant role in the development of estrogen-dependent breast cancer [176]. A clinical study conducted in a cohort of patients with colorectal carcinoma has found that almost 80% of cases are characterized by the presence of leptin receptors in the lesion. This correlates positively with cancer-related angiogenesis and cellular proliferation [177]. The authors suggest that leptin profile could be used to select those patients which are at high risk of developing an aggressive form of colorectal cancer. Sobrinho Santos et al. (2017) have demonstrated in an animal model of oral squamous cell carcinoma that the levels of leptin and its receptor are increased in parallel with HIF-1. However, administration of leptin induces a significant increase in MMP9 and 2, E-cadherin and mir-10 [178]. All of these are known to promote angiogenesis and tumour development.

o. Leucine-Rich Alpha-2-Glycoprotein 1

(LRG1)

Leucine-rich alpha-2-glycoprotein 1 (LRG1) is expressed during the differentiation of granulocytes and it is detected in human neutrophils and in their precursor cells, but not in peripheral mononuclear cells. In patients with non-small cell lung cancer, an increased level of LRG1 was reported in plasma and urine [179, 180]. Increased LRG1 expression is also observed in inflammatory bowel disease correlated with disease activity [181]. LRG1 stimulates angiogenesis via the TGF- β pathway and could have a significant role in cardiac remodelling preventing or attenuating the hemodynamic effects of heart failure [182]. Studies conducted in an animal model have revealed that LRG1 is co-expressed in retinal vasculature along with transforming growth factor- β 1 (TGF- β 1). In this context, LRG1 induces cellular proliferation and angiogenesis. It seems that this molecular pathway is switched on by the binding of LRG1 on endoglin which is the TGF- β 1 receptor. This results in activation of Smad1/5/8 which ultimately results in new blood vessels formation. Moreover, administration of an LRG1 antibody results in the inhibition of angiogenesis. Also, subjects without LRG1 display a significant reduction in pathological retinal angiogenesis [183].

p. NADPH Oxidase1

NADPH oxidase (Nox) family protein consists of seven isoforms (Nox1-5, DUOX1-2) which transport oxygen through the cellular membrane. This leads ultimately to a significant reduction in superoxide oxygen. The isoenzyme Nox 1 is expressed by the epithelial cells, pericytes, osteoclasts, smooth muscle cells and endothelial cells [184]. However, in the resting endothelial cells, Nox 1 is expressed at a low level. Remarkably, Nox 1 level increases significantly after the beginning of angiogenesis. Recent studies have mentioned that the synthesis and release of pro-angiogenic factors such as angiopoietin 1 and VEGF have been shown to be dependent on Nox 1 and Nox2. VEGF, as well as its receptors, VEGFR1 and VEGFR2, are over-expressed in the presence of Nox-1 in both tumour tissues and cell cultures [185, 186]. Vara et al. (2018) have demonstrated that 2-Deoxyribose-1-Phosphate activates NADPH Oxidase 2 which subsequently stimulates angiogenesis via activation of nuclear factor kappa B (NF- κ B) [187].

In-vitro studies have shown that Nox1 modulates apoptosis and morphogenesis of sinusoidal endothelial cells suggests that it might have a significant role in the process of vascular development [184]. Previous experiments have revealed that Nox1 is involved in RAS oncogenic transformation by promoting over-expression of VEGF. Small interference NOX1 RNA inhibits the extracellular signal-regulated kinase (ERK) dependent activation of VEGF promoter (Sp1). Overall, there is a significant decrease in angiogenesis. These effects have been observed in both K-ras transformed kidney cells as well as in human colorectal cancer cells [188]. In a culture of K-Ras-activated kidney cells, transfection of Nox1

small interference RNA (siRNA) decreases angiogenesis and cell migration by blocking NF- κ B dependent matrix metalloproteinase-9 (MMP-9) [189]. Therefore, it is accepted that Nox1 promotes directly the process of angiogenesis. Moreover, increased expression of Nox1 has been reported in clinical cases of colorectal cancer and a recent study has reported that specific inhibitors for Nox4 and Nox2 prevent the development of vascular tumours [184, 186].

q. Urotensin II (Ull)

Ross et al. (2010) reported that urotensin II(Ull) represents a cyclic peptide with a similar structure as somatostatin which binds a special class of G-coupled receptors namely GPR14 or urotensin receptor [190]. Urotensin II (Ull) is expressed in the cardiovascular and respiratory, renal and central nervous system [191]. Recent scientific data suggest that urotensin II (Ull) maintains endothelial cell homeostasis and functionality. At this level, it activates via p38 the extracellular signal-regulated kinase as well as mitogen-activated protein kinase molecular pathways to synthesize IL-8 stimulating angiogenesis. Also, the activation of these molecular pathways would also result in cellular proliferation and endothelial cell survival [192]. However, subsequent to its binding to GPR14 receptors, Ull activates Nox2 and generates reactive oxygen species (ROS). Then a significant increase in HIF-1 α is recorded which further stimulates reactive oxygen species (ROS) production and a major increase in new blood vessels formation via activation of Nox 2 [193].

Molecular evaluation of multiform glioblastoma has indicated that this tumour overexpresses urotensin II (Ull) and its receptor. Subsequent to Ull interaction with its receptors a molecular chain of events culminating with glioma cell migration and adhesion, is activated. This urotensinergic system, which seems to include the G13/Rho/rho kinase pathway and partially the Gi/o/PI3K molecular complex, is noted in glioma tissue resected from patients as well as biopsy tissue and culture cell lines [194]. In breast cancer, urotensin II (Ull) promotes cellular proliferation as well as cancer-related angiogenesis. Moreover, the Thr21Met polymorphism in of the urotensin II (Ull) gene, the UTS2 identifies a group of patients at risk of developing breast cancer [195].

r. Orai-1

The gene labelled Orai-1 encodes a calcium-membrane channel subunit namely CRAC (Ca²⁺release-activated Ca²⁺) which is activated when calcium deposits are low. These types of calcium channels represent the major route for the influx of calcium in T lymphocytes, modulating their immunological response and subsequently activating the transcription factor NFAT [196, 197].

It was claimed by some authors that increased activation of Orai-1 may represent the molecular mechanism which explains the abnormal control of intracellular calcium described in essential hypertension [198]. The Orai-1 channels enable the cells of the retinal pigment epithelium to produce repetitive and/or sustained Ca²⁺ signals necessary for various important functions such as transepithelial transport of various substances, growth factor secretion and phagocytosis [199]. In addition, Orai-1 could have a significant etiopathogenic role in diabetic erectile dysfunction [200].

Smooth muscle cells express Orai-1. However, a congenital deficiency of Orai-1 gene leads to myopathies and chronic lung disease due to bronchial smooth muscle damage. As calcium input is essential in tooth development an Orai-1 deficiency such as in anhidrotic ectodermal dysplasia is associated with anomalies of the enamel development. All of these are described within the setting of reduced T lymphocyte activation and cytokine production. However, the vascular structures in these patients are apparently normal which suggests that Orai-1 is not essential for angiogenesis [201]. Anyway, these results have been contradicted by other studies that have found out that Orai-1 is important in the formation of endothelial tubules, but its functionality is dependent on a prior VEGF-activated Ca²⁺ entry [202]. Moccia et al. (2013) have shown that in early cancer angiogenesis, Orai-1 has a positive role facilitating through the respective channel the calcium influx which stimulates the mobilization of endothelial cells and subsequent angiogenesis [203].

In conclusion, modulation of angiogenesis is possible and new factors have shown promising results in experiments conducted in vitro and in vivo. Often times the authors record puzzling effects such as the anti-tumoral effect of combination Vinorelbine and an anti-angiogenic agent such as Endostar in subjects with non-small cell lung carcinoma in which cancer-associated angiogenesis was not affected [35]. Other studies have revealed important physio-pathological mechanisms which must be further investigated such as the role of Tie-2 in impermeabilization of blood vessels [49]. Other studies have shown that angiogenesis is important in a variety of pathological conditions and theoretically new pharmacological agents could be developed to prevent or treat skeletal malformations, pre-term labour, diabetes and many others. While some of the factors presented above may be acting in parallel, their molecular mechanisms of co-activation and feedback are not yet fully understood. Therefore, more experiments are needed in order to develop efficient pharmacological agents that could effectively modulate angiogenesis in various pathological settings.

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