Biomedicine & Pharmacotherapy 105 (2018) 256–266

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Targeted therapy of chronic liver diseases with the inhibitors of angiogenesis

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ARTICLE INFO

Keywords:
Chronic liver disease
Angiogenesis
Inhibitors
Targeted therapy

ABSTRACT

Angiogenesis appears to be intrinsically associated with the progression of chronic liver diseases, which eventually leads to the development of cirrhosis and related complications, including hepatocellular carcinoma. Several studies have suggested that this association is relevant for chronic liver disease (CLD) progression, with angiogenesis. The fact that angiogenesis plays a pivotal role in CLDs gives rise to new opportunities for treating CLDs. Inhibitor of angiogenesis has proved effective for the treatment of patients suffering from CLD. However, it is limited in diagnosis. The last decade has witnessed a plethora of publications which elucidate the potential of angiogenesis inhibitors for the therapy of CLD. The close relationship between the progression of CLDs and angiogenesis emphasizes the need for anti-angiogenic therapy to block/slow down CLD progression. The present review summarizes all these discussions, the results of the related studies carried out to date and the future prospects in this field. We discuss liver angiogenesis in normal and pathophysiologic conditions with a focus on the role and future use of angiogenic factors as second-line treatment of CLD. This review compiles relevant findings and offers opinions that have emerged in last few years relating liver angiogenesis and its treatment using anti-angiogenic factors.

1. Introduction

Angiogenesis is a process used for organ growth and repair. An imbalance in the process of angiogenesis can lead to several diseases like the malignancy. Angiogenesis is a critical step in several processes including vascular remodeling, tissue damage and wound healing that is required for invasive tumor growth and metastasis. Since the angiogenesis process sets a major role in the control of tumor progression as well as its inhibition, it is also considered as a valuable therapeutic approach for tumor treatment. Chronic liver disease includes viral hepatitis B & C, cholangiocarcinoma, non-alcoholic fatty liver diseases, primary sclerosing cholangitis, primary biliary cirrhosis, hepatocellular carcinoma, and complications of end-stage liver disease. Among them hepatitis C virus (HCV) infection is one of the major cause for the development of hepatic angiogenesis and it plays a critical role in the modulation of hepatic angiogenesis that finally results to hepatocellular carcinoma progression and invasion [1]. Portal hypertension (PH) is a well-known complication of chronic liver disease which determines most complications leading to death or liver transplantation in patients with liver cirrhosis.

Angiogenesis is dynamic as well as hypoxia stimulated and growth factor-dependent process which leads to the formation of new vascular structures from pre-existing vessels [2,3]. This angiogenesis occurs in several organs in response to a pathophysiological alteration. It also plays a major role in the promotion of the etiopathogenesis of several diseases. Angiogenesis is considered as a potential therapeutic target for tumor treatment [4,5]. Hypoxia and inflammation are the main inducers of angiogenesis in the liver and other organs [6,7]. Under hypoxia conditions, angiogenesis is regulated through a mechanism mediated by hypoxia inducing factor (HIF) [8,9] where as its induction during the course of inflammation is regulated through a mechanism mediated by angiogenic cytokines and growth factors [10]. This review is focused to explore the factors associated with angiogenesis and the factors responsible for inhibition of the angiogenesis based on the published literature that could be helpful in the diagnosis of chronic liver disease.

2. Main factors associated with angiogenesis

Based on the past experiences and literature published in the various reputed journals, we found several factors which are associated with angiogenesis (Table 1).

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https://doi.org/10.1016/j.biopha.2018.05.102
Received 27 October 2017; Received in revised form 9 May 2018; Accepted 21 May 2018
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Table 1
Cellular molecules involved in angiogenesis.

Angiogenesis Activators	Actions	Ref.
NO	Stimulates vasodilation	[11]
VEGF family members	Increase vascular permeability; induce EC proliferation; leukocyte adhesion; regulate neo-vessel lumen diameter	[12,13]
VEGF-R, NRP-1	Integrate angiogenic and survival signals	[14,15]
Integrins αvβ3, αvβ5, α6β1	ECM receptors, intercellular communication; mobilized during EC migration; regulate neo-vessel lumen diameter	[16]
Upa	Remodels ECM; releases and activates growth factors	[20]
PAI-1	Stabilizes nascent vessels	[21]
MMPs, heparinases, chymases, tryptases, cathepsins	Remodel ECM; release and activate growth factors	[22–26]
PlGF, aFGF, bFGF, HGF, TGF-α, TGF-β	Induce EC proliferation	[27–29,114]
MCP-1 and other chemokines	Pleiotropic role in angiogenesis	[32–34]
MEF2C	Regulates neo-vessel lumen diameter	[35–37]
Ephrins	Determine branching and arterial/venous specification	[38–40]
PDGF-B and receptors	Recruit pericytes	[41–43]
Ang-1	Stabilizes intercellular contacts; inhibits permeability	[44]
Tie-2	Receptor for Ang-1 and Ang-2	[45]
Ang-2	Ang-1 antagonist (destabilizes vessels; causes EC death)	[46]
TGF-β1, endoglin	Promote vessel maturation, stimulate ECM generation, induce differentiation of mesenchymal cells to pericytes	[48–50,114]
Cyr61, Fisp12	Stimulate directed migration of EC through an αvβ3 integrin-dependent pathway; ECM modifiers, promote EC survival	[51]
IL-18	Angiogenic mediator in rheumatoid arthritis (RA)	[52]
Leptin	Promote cell migration and angiogenesis in rheumatoid arthritis	[53,115]
Del1	Stimulates angiogenesis through integrin binding and is implicated in vasculogenesis	[55]
Follistatin (FS)	Anti-inflammatory and anti-fibrotic properties	[56]
Midkine	Induced a robust antitumor response	[58,59]

2.1. Nitric oxide (NO)

It acts both as an 'actor' of angiogenesis and as a 'director of angiogenesis'. These both functions being expressed during physiological and pathological processes has been reported previously. NO contributes to the prosurvival or proangiogenic program of capillary endothelium by triggering and transducing cell growth and differentiation via endothelial-constitutive NO synthase (ec-NOS) activation, cyclic Guanosine monophosphate (cGMP) elevation, mitogen activated kinase (MAPK) activation and fibroblast growth factor-2 (FGF-2) expression [11].

2.2. Vascular endothelial growth factors (VEGF) family members

The functions of VEGFs are regulating blood and lymphatic vessel development, homeostasis and have the profound effect on neural cells. They are produced by endothelial, hematopoietic and stromal cells in response to hypoxia and upon stimulation with growth factors such as transforming growth factors, interleukins or platelets-derived growth factor [12]. Also previously it has been studied that VEGFR-2 is responsible in regulating endothelial cell migration, proliferation, differentiation and survival as well as vessel permeability and dilation. All these functions of VEGF receptors may give rise to its functional activity. The signal specificity of VEGF receptors were arises from combinatorial activation of multiple cellular pathways. VEGF-C and VEGF-D are the members of VEGF family and are known as lymphangiogenic growth factors. VEGF-C and D plays an important role in tumor lymphangiogenesis that activates VEGF receptor (VEGFR)-3 which are expressed in lymphatic endothelial cells and also mediates its biological activity [13].

2.3. Vascular endothelial growth factors receptors (VEGF-R) and neuropilins (NRP)

Neuropilins-1 and Neuropilins-2 (NRP-1 and NRP-2) are transmembrane glycoproteins with large extracellular regions [14]. Neuropilin-1 is a novel VEGF receptor which participates in the process of modulating VEGF binding to kinase insert domain receptor (KDR) and its bioactivity and also regulates VEGF-induced angiogenesis [15]. Previously it has been reported that NRP mediates the chemorepulsant activity of the collapsin that belongs to a family of transmembrane and secreted glycoproteins.

2.4. Integrins αvβ3, αvβ5, α6β1

Integrins belongs to a family of heterodimeric trans-membrane glycoproteins that mediates cell-cell and cell-Extra Cellular Matrix (ECM) interactions. The αv type of integrins plays an important role in angiogenesis. Different Integrins including αvβ3, αvβ5, αvβ6, α2β1, α5β1, α6β1, and α6β4 involved in cancer growth and invasion. Integrin αvβ3 is mainly expressed on growing blood vessels. It is reported that *in-vivo* angiogenesis in corneal or chorioallantoic membrane model induced by bFGF depends on αvβ3 whereas angiogenesis initiated by VEGF-A depends on αvβ5 [16–18]. Also the development of integrin will be useful in blocking tumor metastasis in patients suffering from cancer. Integrin α6β1 is a laminin receptor that involved to mediate adhesion and migration on laminin matrices in breast carcinoma progression [19].

2.5. Urokinase plasminogen activator (uPA)

Urokinase plasminogen activator (uPA) is a proteolytic enzyme involved in cancer invasion and tumor progression. The urokinase-mediated plasminogen activation system is a complex system of serine proteases involved in angiogenesis. It includes plasminogen or plasmin, activators, inhibitors and cell receptors [20]. Urokinase plasminogen activator is the key enzyme of the initial step of peri-cellular plasmin generation which is produced by cells in its inactive precursor form pro-urokinase.

2.6. Plasminogen activator inhibitor-1 (PAI-1)

Plasminogen activator inhibitor-1 (PAI-1) is the key inhibitor of uPA and tissue-type plasminogen activator (tPA) which plays an important role in the regulation of extracellular matrix remodeling. In blood, PAI-1 is bound to the adhesion protein like vitronectin and is associated

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