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The Role of Endocan in the Development of Hepatocellular Carcinoma

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Abstract Endocan is a dermatan sulfate proteoglycan, constituted of a core protein with 165 amino acids and a single dermatan sulfate chain covalently linked to the serine 137. It is mainly expressed by the activated endothelial cell and regulated by various cytokines and growth factors. In hepatocellular carcinoma (HCC), the expression of endocan increases significantly, and it can induce tumorigenesis and promote the tumor progression. Endocan involves in the proliferation of HCC cell, angiogenesis, metastasis and immunity via a variety of complicated pathways, which cover the regulation of hepatic inflammation-fibrosis-cancer (IFC) axis through nuclear factor-kappa B (NF-κB), modulating cell cycle, interaction with vascular endothelial growth factors (VEGF), the collapse of cell-cell junction, inhibiting of lymphocyte function associated antigen-1 /intercellular adhesion molecule-1(LFA-1/ICAM-1) and changing of tumor microenvironment. Therefore, it is a potential marker and promising therapy target of HCC.

Keywords: *endocan, Hepatocellular carcinoma, NF-κB, vascular endothelial growth factor, lymphocyte function associated antigen-1*

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1. Introduction

Endocan, also called endothelial cell-specific molecule-1 (ESM-1) because of its specifically expressing in human endothelial cells primitively, is a 50kDa compound first cloned from the human umbilical vein endothelial cell (HUVEC) cDNA library by Lassalle and collaborators in 1996 [1,2]. It is confirmed that endocan belonged to proteoglycan (PG) family, and thus the ESM-1 gets the name endocan [2]. Unlike most PG with several glycosaminoglycan(GAG) chains covalently linked to the core protein and participating in the formation of extracellular matrix, endocan is a circulating PG and consists of only one GAG chain connecting with a 20kDa core protein [2,3]. It mainly expresses in the activated endothelial cells and is regulated by various cytokines and angiogenic factors. Further studies reveal that endocan plays important roles in tumor progression and inflammation [3,4]. In HCC, Endocan has been found overexpression in HCC tissue and serum. The expression levels in tumor tissue and serum are closely related to tumor progression and survival. So it may not only be a kind of tumor marker, but also one promising therapy target in HCC. In this review, firstly we describe the basic characteristics of endocan including structure, expression and regulation. Afterwards, the roles of endocan in HCC are discussed in detail.

1.1. Structure of Endocan

Endocan is the product of a single gene that is located in the long arm of human chromosome 5(5q11.2) [1,2]. The gene includes 3 exons and 2 introns [2]. Endocan is an atypical member of PG family and consists of only one GAG chain covalently binding with the core protein [5,6,7]. Initially, only one product of endocan mRNA was recognized by Northern blot. However, Aitkenhead et al. then found there existed a kind of splice variant via RT-PCR, called endocan 2, resulting from endocan mRNA alternative splicing with an internal deletion of the exon 2 [8,9,10]. Except an absence of the sequence encoded by endocan 2 that is related to the phenylalanine-rich region, the isoform has the same N- and C-terminus as endocan. Depontieu and colleagues found non-glycanated and glycanated forms were presence in endocan 2, the binding rate of DS chain joining with the peptide in endocan 2 was 47.4%, and endocan 2 lost the property of promoting tumor growth [10]. The study indicates a lack of amino acids sequence encoded by endocan 2 impairs glycanation, and the phenylalanine-rich region and DS chain play important role in tumorigenesis. Alternative splicing may be a kind of mechanisms to regulate endocan function.

1.2. Distribution and Regulation of Endocan

Endocan can be detected in some other sources of endothelial cell cultured in vitro, including in human coronary artery endothelial cells, human pulmonary artery endothelial cells, human dermal microvascular endothelial cells and human capillary endothelial cells purified from adipose tissues [5]. In the healthy human, endocan mainly expresses in the vascular endothelial cell of lung, kidney and intestinal tract [11]. At first, it was thought that endocan was expressed in endothelial cell exclusively [1]. But later it was found endocan also expressed in epithelial cells of the bronchi, submucosal glands and renal tubular epithelial cells [11]. Wellner et al. found the human adipocyte could express endocan [12]. SM Zhang and colleagues examed the distribution of endocan in normal human tissue by immunohistochemical stains and found that endocan was selectively expressed in actively proliferative or neogeneic tissues and cells such as glandular tissues, endothelium of neovasculature, bronchial epithelium, germinal centers of lymph nodes and so on, but it was not present in silent or resting tissues or cells, for example endothelium of great arteries and spleen [13]. Except expression in normal human tissue, differential expression of endocan has been reported in non-small cell lung cancer [14], bladder cancer [15], glioblastoma [16], renal carcinoma [17,18], colorectal cancer [19] and liver cancer [20]. As a soluble PG, endocan freely circulates in the blood, but the serum level is very low in the normal subject. While it significant elevates under pathological conditions of inflammation [4,21,22] and a variety of tumors [14,17,19,20,23].

Endocan is regulated by numerous factors, such as cytokines, growth factors, tumor microenvironment, transcription factors. Tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) have been shown to upregulate endocan expression in vitro. INF-γ and IL-4 do not have any effect when using alone, but INF-γ inhibits the upregulation of endocan induced by TNF-α [1,11]. A combination of VEGF and hepatocyte growth factor (HGF) can cooperatively upregulate of endocan gene [24]. Latter studies shows that VEGF alone can promote endocan expression through the PKC/NF-κB signaling pathway, while PI3K-AKT-forkhead axis plays an inhibitory role [18,25]. One study found fibroblast growth factor-2 (FGF-2) could stimulate the production of endocan in vitro [16], but two others found that FGF-2 did not alter endocan expression [15,18]. Endocan gene was upregulated twofold in the human trabecular meshwork cells with transforming growth factor(TGF)-β1 and -β2 treatment [26]. Lipopolysaccharide (LPS) induces sustained release of endocan [21,27]. In addition to these, positive regulation factors include hypoxia and hypoxia inducible factor-1α (HIF-1α) [16,28], PKC activator phorbol ester [18]. Rong Cong et al. demonstrated that Hhex was directly bound to an evolutionarily conserved Hhex response element (HRE) 1 and suppressed the expression of endocan, which indicated that Hhex acted as a transcriptional repressor of endocan [6]. Another study shown that protein PI3K had an similar inhibitory effect on Hhex because of endocan expression increased 12-fold after suppression of PI3K with LY294002 [18].

2. Endocan in HCC

2.1. Endocan in Chronic Liver Disease, Liver Fibrosis and Liver Cirrhosis

HCC patients in China usually undergo the process of chronic liver disease, especially chronic hepatitis B, which leads to liver fibrosis and cirrhosis before progressing to HCC. Serum endocan levels in chronic hepatitis and liver cirrhosis are much higher than that in normal subject [20,29]. And endocan regulated by many cytokines and growth factor takes part in inflammatory disorders [1,11,24,27]. Thus, it may play a role in the hepatic IFC axis. In vitro, endocan can activate NF-κB [27], which plays a central role in the hepatic IFC axis. The apoptosis and necrosis of hepatocytes induced by kinds of chronic liver disease result in activating of Kupffer cells, then activating NF-κB, which can induce proinflammatory cytokines expressing, including TNF-α and IL-6. Various proinflammatory cytokines activate NF-κB on hepatocytes and hepatic stellate cells (HSCs). In the hepatocytes, the activation of NF-κB inhibits cell apoptosis and induces cell proliferation, while in the HSCs, it results in hepatic fibrosis and subsequent HCC [30]. Besides, endocan and TNF-α can promote each other [1,11,27], and TNF-α plays an important role in the activation of HSCs and Kupffer cells in liver fibrosis [31,32]. On the other hand, Carrillo et al. found endocan was involved in endothelial-mesenchymal transition (EndoMT) [33], which had been implicated in the pathogenesis of fibrosis in various organs, such as heart fibrosis [34], kidney fibrosis [35], pulmonary fibrosis [36]. Accordingly, endocan may facilitate liver fibrosis through mediating the EndoMT process. Interestingly, endocan may play a part of anti-liver fibrosis since it can bind with HGF and active HGF/c-MET pathway [2] which has an anti-hepatic fibrosis effect through inducing apoptosis of HSCs and encouraging hepatocyte regeneration [37,38]. Besides, the activiation of NF-κB can inhibit hepatocyte apoptosis and induce cell proliferation [30].

Endocan is mainly expressed by the vascular endothelial cells, and represents a new marker of endothelial cell activation [11]. It has been proved that endocan expression is related to diseases characterized by endothelial cell activation or dysfunction. Scherpereel et al. reported that blood level of endocan in patients with sepsis was related to severity of illness and outcome of patient, which might represent endothelial dysfunction [21], Li et al. demonstrated that endocan expression reflected the degree of endothelial cell injury in renal allografts [39]. Balta et al. found patients with Behcet disease had significantly higher serum levels of endocan which positively correlated with activity of disease [40], Adekola et al. showed plasma endocan concentrations increased in patient with preeclampsia [41] and untreated essential hypertension. Serum endocan levels were positively correlated with carotid intima–media thickness (cIMT) [42]. Further study revealed endocan activated endothelial cells and led to endothelial cells dysfunction via enhancing the vascular permeability, disrupting cell-cell junction, increasing the level of chemokines, promoting the release of VEGF and facilitating the binding of VEGF-A to VEGF receptor-2 (VEGFR-2) [27]. As a consequence,

endocan may be a surrogate endothelial dysfunction marker and plays a functional role in endothelium-dependent pathological disorders. Endothelial dysfunction in the intrahepatic and extrahepatic microcirculation plays pivotal roles in the development of liver cirrhosis [43]. The serum endocan level increases significantly in patients and rats with liver cirrhosis [20,29,44]. And increased endocan exacerbates endothelial activation and dysfunction. In the intrahepatic microcirculation, liver sinusoidal endothelial cells (LSECs) dysfunction impairs endothelium-dependent relaxation and contributes to increased intrahepatic vascular resistance [43]. In the extrahepatic, microcirculation endocan induces VEGF and facilitates the binding of VEGF-A to VEGFR-2 [27,45]. On the one hand, VEGF signal can induce endothelial nitric oxide synthase (eNOS) expression and activation to increase the production of nitric oxide (NO), resulting in vasodilatation and thinning of arterial in splanchnic and systemic circulation. On the other hand, it contributes to collateral vessel formation [43]. Hence, Endocan takes part in the formation and progression of port hypertension in liver cirrhosis.

To sum up, endocan can accelerate the formation and progression of liver fibrosis, cirrhosis and induce the occurrence of HCC in the long term through regulating the hepatic IFC axis and EndoMT. Besides, it can worsen port hypertension because of its ECs dysfunction as well. However, Tok et al. revealed that the serum endocan concentrations of chronic hepatitis B, chronic hepatitis C and non-alcoholic fatty liver disease were significantly lower than those in normal control, further they found no correlation between the level of serum endocan and the degree of liver fibrosis according to the METAVIR stages [46]. Therefore, more studies are needed to understand the relationship between endocan and chronic liver disease, liver fibrosis and cirrhosis.

2.2. Endocan in the Growth of HCC

One study observed a positive correlation between endocan expression level in HCC tissue and the size of tumor [47]. Ozaki et al. found elevated serum endocan levels were significantly associated with a greater number of tumors [29]. An experiment demonstrated that tumor cells overexpressing endocan formed tumor after injected into severe combined immunodeficient (SCID) mice, and circulating levels of endocan correlated positively with tumor size. While using anti-endocan monoclonal antibody MEP08 block endocan could slow the growth rate of tumor in SCID mice [48]. Through these above, endocan plays a positive role in tumor growth, and the potential mechanisms follows.

Kang et al. [20] found in vitro the viability of endocan siRNA-expressed SK-Hep1 cells was decreased in comparison to the control siRNA-expressed cells. And the increasing phospho-IκB and reducing NF-κB p65 expression levels was observed. Thus endocan can increase the survival rate of cancer cell of HCC via IκB-dependent NF-κB pathway. Beyond these, Kang et al. [20] further revealed that in the SK-Hep1 cell lines of endocan gene silencing, the cell cycle was arrested at G1/S phase, the level of cyclin D1 and cyclin-dependent kinase 4 (CDK4) decreased. As a result, endocan is able to modulate the cell cycle progression via the regulation of cyclin D1/CDK4 complexes by PTEN in hepatocellular carcinoma cells. In addition, the DS chain of endocan can bind to HGF, activate HGF and promote the mitogenic activity [2]. So endocan may induce HCC growth by means of activating HGF-cMET pathway.

2.3. Endocan in the Angiogenesis of HCC

HCC is a kind of solid tumor with abundant vascularity, and tumor vascular is crucial for the growth and progression of HCC. The previous study showed that endocan mRNA and protein were overexpressed in HCC tumor vessels, and the endocan mRNA level was correlated to microvascualr density (MVD) stained by CD34, vascular invasion [49]. Another study found the similar consequence by immunohistochemistry that was MVD denoted by endocn was correlation with microscopic venous invasion and MVD denoted by CD34, a pan-endothelial cell marker [50]. Besides, significant correlation between serum endocan and vascular invasion was found by Ozuki and colleagues [29]. All these above suggest a connection between endocan and angiogenesis in HCC. Positive correlation between endocan expression and vascular endothelial growth factor expression in HCC tissue was found [49,50]. And more than one evidences demonstrated endocan and VEGF can influence each other [9,15,25,27,45]. Overexpression of VEGF had been found in HCC [51,52,53], and two meta-analysis pointed out there was a correlation between the level of VEGF expression and poor survival rate [54,55]. VEGF and its receptors play crucial roles in tumor angiogenesis. VEGFR-2 is predominantly responsible for responses of vascular endothelial cells to VEGF, and stimulating VEGFR-2 promotes growth, migration, and tubular formation of endothelial cells [56]. Silencing of endocan in blood endothelial cells inhibits VEGF-A–induced tube formation, migration, and VEGFR-2 phosphorylation [15]. A positive feedback loop exists between endocan and VEGF [15,45], in which VEGF binds withVEGFR-2 and stimulates endocan expression depending on activating of PKC-NF-κB.

Sprouting is one of the mechanisms through which HCC acquire new blood vessel. Tip cells, filopodias on it and stalk cells join in the process [58]. Studies showed that endocan expressed in endothelial tip cells [15,57,59]. And Toro et al. pointed out endocan–alkaline phosphatase (AP) bounded to stalk cells at the vascular front, which indicated that endocan maight selectively act on stalk cells to regulate angiogenesis [57]. In addition, Rocha et al. observed the filopodias reduced significantly in endocan gene knockout mice, which manifested endocan maight regulate angiogenesis through controlling the filopodias emission [45]. Aitkenhead et al. shown that endocan in tubes was almost four times greater than that in the two-dimension endothelial cells, which suggested that endocan promoted tube formation in angiogenesis [9].

In HCC, endocan mRNA and protein expression increase significantly. The increase of endocan mRNA and protein expression facilitates the VEGF-VEGFR-2, which in turn induces endocan expressing, and enhance VEGF-VEGFR-2 mediated angiogenesis. On the other hand, endocan may directly promote sporting. And lastly, higher endocan makes the tube form easily during angiogensis in HCC.

2.4. Endocan in the Metastasis of HCC

It is very important that changing of vascular permeability for HCC metastasis. And weakening cell-cell junction of vascular endothelial cell is necessary for HCC cells to cross the endothelial barrier [60]. Lee et al. shown that endocan had effect on cytoskeletal rearrangement and disrupting the interendothelial junctions [27,60]. Endocan could increase the phosphorylated myosin light chain, and significantly decreased levels of ZO-1 and occludin in vitro [27]. Besides, endocan could activate NF-κB that altered the distribution of TJ proteins. Adherence junction disruption is associated with the activation of Rho and the deactivation of Rac, and endocan can inactivate Rac and activate Rho [27]. Study found endocan in vitro could increase tyrosine phosphorylation of the VE-cadherin that involved in breaking adherence junctions [27]. Moreover, endocan induces the expression of VEGF-A and facilitate the binding of VEGF-A to VEGFR-2, which can weaken the tight junction and adherence junction through a variety of ways, such as activating sequentially of Src, ERK, JNK, and PI3K/Akt leading to ZO-1 and occludin phosphorylation, activating PKC resulting in the TJ disassembly, phosphorylating the intracellular components of AJ and so on [27,60]. In brief, endocan leads to or promotes the dissociation of cell-cell junctions in ECs by multiple avenues, and hence increases the vascular permeability. In addition, endocan induces cell adhesion molecules (CAMs) express in ECs [27], which facilitates HCC cell extravasation.

Endocan can directly accelerate the migration and invasion of HCC as well. One study [20] showed the cell migration rate of endocan siRNA-expressed HCC cells decreased 1.6-fold in 24 h compared with the control siRNA-expressed HCC cells in vitro. And then they measured invasive cell in SK-Hep1 cells migrating through matrigel in invasion chamber, and found a 2.2-fold decreasing of the cell invasion rate in invasive cells expressing ESM-1 siRNA.

It has been proved that lymphatic metastasis is one of tumor spread ways. Reportedly, in HCC, Lymphatic vessel endothelial hyaluronan receptor-1 and Prox 1-positive lymphatic vessels are abundant nearby the tumors, and lymphangiogenesis promotes metastasis [61]. Shin et al [62] revealed endocan in vitro could increase the stimulatory effects of both VEGF-A and VEGF-C on lymphatic endothelial cell proliferation and migration that contribute to lymphangiogenesis. Therefore, endocan may invigorate lymphatic metastasis in HCC.

2.5. Endocan in Immunity of HCC

The activation of T cells depends on two kinds of signals: the first one is the binding of MHC/ peptide on antigen-presenting-cells (APC) or target cells with TCR/CD3 complex on T cells. The second one, also called co-stimulatory signal, is the binding of co-stimulatory molecules on the APC or target cells with their receptors presenting on T cells. When absence of co-stimulatory signal, the first one can't induce proliferation and secreting cytokine of T cells alone, resulting in anergy of T cells [63]. Lymphocyte function associated antigen-1 (LFA-1)/intercellular adhesion molecule-1(ICAM-1) is one of co-stimulatory molecules [63]. With the co-stimulation of LFA-1/ICAM-1, the activities of T cells significant increase, including higher production of Th1 cytokines, stronger proliferating response and more strengthening of T cell cytotoxicity [63]. Secondly, LFA-1/ICAM-1 is a pair of adhesion molecules as well and thereby plays an important role in migration, adhesion and recruitment of lymphocytes [64]. And among the two, LFA-1 plays a pivotal role in controling the $CD8^+$ T cells recruitment into the tumor tissue in HCC [65]. Béchard et al. found endocan was a ligand of LFA-1, which could bind with LFA-1 and change the configuration of LFA-1 to inhibit LFA-1/ICAM-1 interactions [66]. According to these above, endocan has a negative impact on HCC immunity via harming the recruitment of circulating lymphocytes to target sites and LFA-1-dependent leukocyte migration and adhesion, and more importantly weakening the adaptive immunity of T cells in HCC patients through down-regulating the co-stimulatory signal of LFA-1/ICAM-1.

However, there are some opposite results observed in two studies. Lee et al. found endocan could enhance the migration of monocytes in vitro and intensify the transmigration of leukocytes to the peritoneal cavity in mice [27]. Furthermore, Rocha et al. observed that the absence of endocan impaired leukocytes extravasation [45]. And these may ascribed to the following two reasons: First one is that endocan can increase vascular permeability [27,45], the other is endocan induces the expression of cell adhesion molecules (CAMs) [27]. But more need to be done to know whether there are some positive influences of endocan on HCC immunity.

2.6. Endocan and Tumor Microenvironment in HCC

The tumor behavior is affected not only by the genetic of tumor cell, but also by the surrounding milieu. This surrounding milieu, also called tumor microenvironment, is necessary for survival, growth, proliferation, and metastasis of tumor cell. Its changing could deeply impact on the tumor behavior. The HCC microenvironment is constituted of cellular elements, cytokines, growth factors, several proteins, and physical environment [67]. Cancinoma-associated fibroblasts (CAFs) are central component of tumor microenvironment. In HCC, CAFs are involved in tumor growth and invasion through producing abundant growth factors, cytokines and some other elements [67]. Carrillo et al. found endocan participated in EndoMT [33], by means of which, resident endothelial cells acquired invasive and migratory properties [68]. Zeisberg et al. revealed that EndoMT was one important source of CAFs [69]. In another aspect, it is well-known that various cytokines and growth factors regulate the express of endocan. While endocan can reciprocally induce some of them expressing [27], such as TNF-α, IL-8, VEGF, cell adhesion molecules and so on. Besides, the physical environment hypoxia and hypoxia-inducible factor-1α (HIF-1α) induce endocan expression [16,28], and this involve in many pathways in HCC. Thus, through influencing diversified elements in HCC microenvironment, endocan disturbs the behavior of HCC.

2.7. Endocan: A Potential Marker and Therapy Target in HCC

In HCC tissue, endocan mainly expressed in tumor endothelial cell, and endocan expression in HCC tissue on both protein and RNA level is higher than that in corresponding noncancerous hepatic tissues [20,47,49,50]. Also serum endocan levels in HCC are much higher than that in the healthy one, acute hepatitis, chronic hepatitis and liver cirrhosis (LC) [20]. And because of endocan as an accomplice in HCC progression, it may be a potential HCC biomarker. Ozaki et al. [29] pointed out as the serum level of endocan 3.59ng/ml a cut-off, it could discriminate HCC and LC with 54.7% sensitivity and 86.8% specificity. But Charles et al. [70] found no significant difference between early HCC and alcoholic cirrhosis. Besides, endocan elevates in patients with other tumors or sepsis as well [3,4,21,22]. As a consequence, it is debatable to use endocan for HCC diagnosis. But serum endocan levels are related to the Child-Pugh grade [29,70], the number of tumor [29], the vascular invasion [29], and the cancer embolus of portal vein [70]. And close correlations between endocan expression in HCC tissue and the vascular invasion [20,47,49,50], as well as the tumor size [47] have been observed. The higher Child-Pugh grade, more numbers and bigger size of tumor, the presence of vascular invasion and portal vein tumor thrombus are poor prognostic factors in HCC [71,72,73,74,75]. Thus, serum endocan, endocan expression in HCC tissue can be a marker of HCC progression and prognosis. The result of the higher of serum endocan level or endocan expression in HCC tissue, the poorer prognosis of HCC patients is proved in several trials [29,47,50,70]. It is controversial between serum endocan level and tumor recurrence of HCC. On study found no statistically significant existed between the serum endocan level and tumor recurrent after curative treatments and RFA [29]. However, Zoli et al. [47] revealed endocan expression was an independent predictive factor of early and overall recurrence in early HCC after RFA, and showed that the stratification according to baseline serum AFP and endocan stain in HCC tissue might provides a better choose of appropriate candidates for liver transplantation following RFA.

What's more important is endocan can be a promising therapy target because of its promoting angiogenesis, tumor cell proliferation and metastasis, inhibiting immunity, and changing tumor microenvironment in HCC. Kang and colleagues [20] found endocan silence decreased cell survival, migration and invasion and arrested the cell cycle in Sk-Hep1 cell. The splice variant endocanΔ2, impairing the glycanation and the absence of the sequence encoded by exon2, lose tumorigenic properties [10]. And endocan monoclonal antibody MEP08, which can block the phenylalanine-rich region of endocan core protein, inhibits the tumor growth in animal experiment [48]. Pretreatment of blood endothelial cells with a VEGFR-2–blocking antibody inhibited induction of endocan expression [14,15]. PI3K-AKT signal pathway and transcription factor Hhex can inhibit endocan expression [6,25]. INF-γ can inhibit the positive effect of TNF-α on endocan [1,11]. It is possible to inhibit endocan expression or block endocan via the ways above, which may be further used to control the HCC progression.

3. Conclusion

In summary, endocan acts as a roll booster in HCC genesis and progression. In the chronic liver disease, it takes part in EndoMT process and regulates the hepatic inflammation-fibrosis-cancer axis via activating NF-κB and affecting various proinflammatory factors. Through which, endocan facilitates the formation and development of liver fibrosis, cirrhosis and the occurrence of HCC ultimately. In HCC, endocan promotes the proliferation of tumor cell, tumor angiogenesis and metastasis, and interferes in the immunity and tumor microenvironment. The activation of IκB-dependent NF-κB pathway and HGF-cMET axis, the disorder of cell cycle are the main mechanisms of endocan in tumor cell proliferation. A positive feedback loop exists between endocan and VEGF, which promote each other resulting in tumor angiogenesis and lymphangiogenesis. Besides, endocan can also promotion of sprouting and tube-formation during angiogenesis. While in the HCC metastasis, endocan can increase vascular permeability through disrupting cell-cell junction, and directly accelerate the migration and invasion of tumor cell. LFA-1/ICAM-1 is a co-stimulatory signal for activation of T cells, and the attenuation of co-stimulatory signal weakens the immunity because of endocan binding to LFA-1 and then inhibiting LFA-1/ICAM-1 interactions. In addition, elevated endocan in HCC leads to the increasing of CAFs and the changing of some other elements in tumor microenvironment, which can play complex roles in HCC. As a potential marker, Endocan is useful for predicting prognosis. More attractively, endocan can be a promising therapy target in consideration of its positive roles in HCC progression. Maybe the inhibition of endocan is an effective therapeutic strategy for HCC treatment.

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