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Endocan as a Biomarker of Endothelial Dysfunction in Cancer

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Abstract

Endocan also called endothelial cell-specific-molecule-1 is a product of endothelial cells, highly regulated by vascular endothelial growth factor and expressed during the switch between dormant to fast-growing angiogenic tumors. No other molecule is currently known to be a read out of endothelial activation and dysfunction in tumor progression. We here reviewed the present knowledge about endocan that present clinical value as a tissue- and blood- based prognostic and potentially as a companion biomarker in cancer. By immunohistochemistry endocan was shown to be overexpressed into endothelial cells of small and large vessels in lung, kidney and brain tumors. High endocan serum levels were shown to be significantly correlated with the presence of metastasis and with limited survival in kidney and lung cancers. Moreover, endocan release by endothelial cells was *in vitro* modulated by addition of anti-angiogenic compounds. At a time where biomarkers are hugely needed to improve anti-angiogenic targeted treatments, endocan could be a pertinent biomarker to select patients and/or to clinically monitor the efficacy of cancer drugs. Through its awaited functional applications, endocan appears today as a promising biomarker to access to personalized medicine and to optimize therapy cost / benefit ratio.

Keywords: Endocan; ESM-1; Biomarker; Diagnosis; Angiogenesis; Endothelial dysfunction; Personalized medicine; VEGF

Abbreviations: AML: Acute Myeloid Leukemia; ATRA: All-Trans Retinoic; ESM-1: Endothelial cell-Specific Molecule-1; DS: Dermatan Sulphate; FGF-2: Fibroblast Growth Factor 2; HS: Heparan Sulphate; HGF/SF: Hepatocyte Growth Factor/ Scatter Factor; HUVEC: Human Umbilical Vein Endothelial Cells; ICAM-1: Intercellular Adhesion Molecule-1; LFA-1: Lymphocyte Function-associated Antigen-1; MVD: Microvessel Density; NK: Natural Killer; VEGF: Vascular Endothelial Growth Factor

Introduction

A need of biomarker in cancer

Angiogenesis is recognized to play a critical role in the development of hypervascular tumors such as lung carcinomas, clear cell renal carcinoma and glioblastomas, three cancer types among the most frequent in aged patients. Over 60 trillion endothelial cells make up the largest interconnected network in the human body and clearly tumor growth depend on a vascular supply and generation of new blood vessels (Folkman and Klagsbrun, 1987; Carmeliet, 2005; Aird, 2007; Kerbel, 2008). Endothelial cells in tumors may not have the appearance of normal endothelial cells as they are disorganized, loosely connected, branched, sprouting and forming a defective cellular lining of the vessel wall (Folkman, 1971; Carmeliet, 2005). Biomarkers that specifically react with the endothelial cells of angiogenic tissue have rapidly appears of great interest especially when biomarkers of tumor cells are not available or when an endothelium-targeted treatment is associated with chemotherapy.

The prognostic value of angiogenesis associated endothelial biomarkers has been investigated both on tissue sections and in the blood stream of cancer patients. Those potential markers include assessment of microvessel density (MVD) on tissue sections, blood cytokine levels such those of vascular endothelial growth factor (VEGF) or of soluble receptors (VEGFR). In most of the reviewed literature, MVD is evaluated by antibodies against pan-endothelial cells, such as the anti-CD31, -CD34, or -von Willebrand factor antibodies. However, these antibodies today used to classify tumor-associated blood vessels as mature, intermediate and immature blood vessels, labeled not only endothelial cells (since for instance, CD34 is expressed on majority of hematopoietic stem/progenitor cells, bone marrow stromal cells, capillary endothelial cells, lymphatic endothelial cells, embryonic fibroblasts, and some nervous tissue), they showed heterogeneity in their expression (for instance, CD34 is a pan-endothelial marker of microvascular endothelial cells, but is not expressed by most large vessel endothelial cells) and these antibodies may label not only newly formed vessels but also normal vessels within tumor tissues (Fina et al., 1990; Fiedler et al., 2006; Folkman et al., 2006).

VEGF has been largely documented since its discovery, as a major player of angiogenesis by virtue of its ability to induce

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vascular permeability, to induce and sustain endothelial cell division and survival, and to initiate the sprouting of new blood vessels required to supply tumors with oxygen and nutrients (Folkman and Klagsbrun, 1987; Plouet et al., 1989; Ferrara and Henzel, 1989; Folkman, 2006). The hypothesis that tumor progression can be arrested by anti-VEGF approaches has been studied experimentally over thirty years and several drugs have come to the clinics (Folkman, 1971; Folkman, 2006; Kerbel, 2008). For example, antibodies such as bevacizumab that neutralize VEGF biological activity have shown a longer progression-free survival time in patients with metastases in clinical trials (Kerbel, 2008). Small molecule multikinase inhibitors such as sorafenib or sunitinib have also demonstrated activity in the control of metastatic diseases (Folkman, 2006; Kerbel, 2008).

However, the survival benefits of these targeted treatments are still relatively modest (usually measured in months) in aggressive cancers such renal carcinoma and lung cancers. Not all the patients respond to these drugs and as observed in preclinical models, there have been concerns that anti-VEGF therapies increase hypoxia and thereby treatment resistance (Bergers and Hanahan, 2008). Predictive biomarkers for the efficacy of these new anti-angiogenic treatments have been currently elusive and no endothelial focused and reliable biomarker is available. Current studies on endothelial biomarkers are focusing on circulating endothelial progenitor cells as predictive blood markers. However, they are very demanding techniques and clear results are still pending (Bertolini et al., 2007).

Endocan also called endothelial cell specific molecule-1 (ESM-1) has been reported as specific of endothelial tumor cells and was shown to be expressed by tip cell during angiogenesis process (Lassalle et al., 1996; Sarrazin et al., 2006; Abid et al., 2006; Recchia et al., 2010; Strasser et al., 2010). Moreover, the presence of endocan in the blood flow has been shown to be strictly reflecting the vascular integrity and the health of the body vasculature as validated in sepsis where endothelium is clearly challenged (Bechard et al., 2000; Scherpereel et al., 2006). The capability to monitor patient response through the read out of the vascular integrity can be useful to identify drugs that may benefit to specific populations of cancer patients. No other molecule is currently available to be a read out of endothelial activation and dysfunction in tumor progression. We will here review the present knowledge about endocan that presents a clinical value as a tissue- and blood-based prognostic biomarker and potentially as a companion biomarker for anti-VEGF therapies.

What is endocan?

Endocan/ESM-1 was originally discovered as a soluble product of endothelial cells grown in culture (Lassalle et al., 1996). Structurally endocan is a cystein-rich proteoglycan carrying a single chain of dermatan sulfate and exhibiting an apparent molecular weight of 50 kDa (Bechard et al., 2001a; Delehedde et al., 2006). Degradation by the specific glycosaminoglycan depolymerising enzyme chondroitinase ABC *in vitro* reduced the size of secreted endocan from approximately 50 kDa to 20 kDa, the latter size corresponding by SDS polyacrylamide gel electrophoresis to the deglycosylated core protein (Bechard et al., 2001a). The secreted, blood borne endocan was shown to be in the proteoglycan form in human sera (Bechard et al., 2000; Bechard et al., 2001a; Bechard et al., 2001b; Scherpereel et al., 2003; Delehedde et al., 2006; Sarrazin et al., 2006).

Interestingly, endocan is highly upregulated by pro-angiogenic molecules such as VEGF of fibroblast growth factor (FGF-2) that are both mediators involved in angiogenesis and cancer progression (Grigoriu et al., 2006; Sarrazin et al., 2006; Abid et al., 2006; Rennel et al., 2007; Maurage et al., 2009; Leroy et al., 2010). More recently, Shin et al. have shown that endocan was one of the genes that were most potently induced by both VEGF and VEGF-C in human dermal lymphatic endothelial cells (Shin et al., 2008). By in situ hybridization studies, endocan was also shown to be preferentially expressed by tumor vasculature in mouse xenograft models (Abid et al., 2006).

Functions of endocan

The main function of endocan has been shown to inhibit the interaction between intercellular adhesion molecule-1 (ICAM-1) and the integrin (lymphocyte function-associated antigen-1) LFA-1 on lymphocytes and monocytes (Bechard et al., 2001b) and therefore affect LFA-1 mediated leukocyte functions, such as the firm adhesion of leukocytes to the endothelium and the leukocyte migration itself into tissues (Bechard et al., 2001b; Tissier et al., 2004; De Freitas et al., 2009). Interaction between ICAM-1 and LFA-1 has also been implicated in the binding of cytotoxic lymphocytes and natural killer (NK) cells to tumor cells. Endocan was recently shown to dose-dependently inhibited migration in transmigration endothelial assays of NK cells that reside naturally in the vasculature (De Freitas Caires et al., 2009). Furthermore, endocan was shown to promote *in vitro* the mitogenic and promigratory activity of VEGF, HGF/SF and VEGF-C (Bechard et al., 2001a; Sarrazin et al., 2006; Shin et al., 2008) whereas addition of endocan alone did not affect endothelial cell functions. This role was mainly suggested to be due to glycan moieties of endocan that can bind heparin-binding factors (Bechard et al., 2001a; Scherpereel et al., 2003; Sarrazin et al., 2006). Endocan was also described as one of a main mediator of lymphangiogenesis since VEGF or VEGF-C induction of proliferation and migration of lymphatic endothelial cells were both significantly inhibited by siRNA-mediated silencing of endocan *in vitro* and *in vivo* (Shin et al., 2008).

Endocan as a marker of endothelial activation

All the cultured human endothelial cells that were tested from different origins (including coronary, pulmonary artery dermal and capillary endothelial cells) and that were grown in serum-rich culture media, have been shown to express endocan transcripts or proteins (reviewed in Sarrazin et al., 2006). However, highly vascular organs like brain, liver and heart were not identified as expressing endocan (Lassalle et al., 1996; Aitkenhead et al., 2002), suggesting that endocan is not expressed by resting endothelial cells and leading investigators to propose endocan as a marker of endothelial activation.

Recently, endocan/ESM-1 was identified to be one of the genes involved in the switch from dormant to angiogenic tumors (Almog et al., 2009). In mouse xenograft models of human breast cancer, glioblastoma, osteosarcoma and liposarcoma, the

conversion of dormant tumors to exponentially growing tumors was shown to be highly correlated with regulation and activation of endocan gene (Almog et al., 2009). This increase of endocan gene expression was particularly high in glioblastoma and liposarcoma models (by a 30-fold increase). Endocan was significantly elevated in all angiogenic fast-growing tumor cells the authors have analyzed (Almog et al., 2009). When overexpressed in human embryonic kidney 293 cells, endocan was previously found to promote tumor growth in a mouse xenotransplantation model (Scherpereel et al., 2003; Depontieu et al., 2008). Strasser et al. have recently demonstrated by microarray analysis that endocan is highly specific to tip cells, the specialized subset of endothelial cells known to mediate vessel growth and to be responsive to VEGF (Strasser et al., 2010). In this particular study, CXCR4, angiopoietin-2 and apelin were also shown with endocan to be enriched in tip cells (Strasser et al., 2010). Furthermore in animal models, Recchia et al. (2010) have also identified endocan with apelin as the main genes involved in the angiogenic switch occurring during retinal neovascularization (Recchia et al., 2010).

Endocan as a prognostic biomarker in cancer?

Being expressed specifically by endothelial cells, a role for endocan was suggested during tumor angiogenesis (reviewed in Sarrazin et al., 2006). Gene expression studies of tumor and endothelial cells by large microarray studies have been since picking up endocan as one of the gene the most overexpressed in various types of cancer from lung (Borczuk et al., 2004), breast (van 't Veer et al., 2002), thyroid (Wattel et al., 2005 ; Lacroix et al., 2005), ovary (Buckanovich et al., 2007) and kidney (Aitkenhead et al., 2002; Amatschek et al., 2004; Lenburg et al., 2003; Cifola et al., 2008). Using specific antibodies against human endocan, a marked overexpression of endocan was described in the cytoplasm of endothelial cells of the tumor vessels in cancer of the lung (Scherpereel et al., 2003; Grigoriu et al., 2006), brain (Maurage et al., 2009) colon (Zuo et al., 2008), liver (Huang et al., 2009) and in clear cell carcinomas of the kidney (Rennel et al., 2007; Leroy et al., 2010).

Endocan overexpression in cancer

Immunohistochemical analysis of lung tumors revealed that the intratumoral vessels exhibit endothelial staining for endocan with expression present in most of the vessels identified by anti-CD34 staining (Grigoriu et al., 2006). By RT-PCR, the authors showed that endocan and VEGF mRNA expressions were positively correlated (Grigoriu et al., 2006). Large gene expression studies have previously shown that endocan overexpression was correlated with the overexpression of angiogenic molecules such as VEGF, VEGFR or c-met in various types of cancers including lung cancer (reviewed in Sarrazin et al., 2006). As VEGF induce a sustained increase in both endocan mRNA and protein in primary cultured human endothelial cells, endocan overexpression observed in lung tumor vessels may be considered as a consequence of local VEGF expression in tumor microenvironment.

In high-grade gliomas also called glioblastomas (n=42), endocan immunoreactivity has always been detected in endothelial cells within the tumor and those at the margins of the tumors (Maurage et al., 2009). Endocan was never detected in the cerebral cortex distant from the tumors and endothelial cells are mostly all endocan negative in low-grade gliomas (grade I and grade II). Therefore in brain tumors, endocan expression is associated with a higher grade and with the abnormal vasculature reflecting neoangiogenesis in glioblastomas (Maurage et al., 2009).

In hepatocarcinomas, endocan protein was expressed in endothelium in all specimens issued from a series of 100 patients but was not expressed in endothelium of normal liver tissue (Huang et al., 2009). In this particular study, microvessel density denoted by endocan was correlated with microscopic venous invasion and VEGF expression (Huang et al., 2009). When the authors studied the correlation between endocan-microvascular density and the expression of VEGF, they found that the density of endocan immunoreactive microvasculature was closely correlated with VEGF expression (Huang et al., 2009). Endocan could therefore represent a biomarker of endothelial cell activation in response to pro-angiogenic signals in hepatocarcinoma.

Another interesting example on the potential of endocan as a biomarker came over analysis of its expression in tissues issued from renal cancer patients (Leroy et al., 2010). By immunohistochemistry, endocan is detected in the cytoplasm of endothelial cells in clear cell renal carcinoma, decorating each small and large intratumor vessels, but never detected in blood vessels distant from the tumor (Leroy et al., 2010). Using immunohistochemistry and RT-PCR, Leroy et al. (2010) demonstrated that endocan is weakly or not expressed in papillary carcinomas. This finding is of interest, because clear cell renal carcinoma and papillary carcinomas have different molecular pathways. The clear cell renal carcinoma molecular pathways is characterized by the inactivation of the gene product of Von Hippel-Lindau by mutation, deletion or promoter methylation, leading to the stabilization of hypoxia inducible factor 1 and consecutive increase in the transcription of VEGF target genes. The molecular pathways of papillary carcinoma are still only partially known: a duplication of chromosome 7 is however frequently found and may lead to activation of the c-met pathway.

Endocan expression as a bad prognosis signature

Gene expression studies have rapidly revealed the potential of endocan as a gene of bad prognosis signature in various types of cancer from lung (Borczuk et al., 2004), breast (van 't Veer et al., 2002), ovary (Buckanovich et al., 2007) and kidney (Amatschek et al., 2004; Lenburg et al., 2003; Cifola et al., 2008).

Interestingly, in glioblastoma patients, endocan immunoreactivity within endothelial cells clearly correlated with a shorter survival (Maurage et al., 2009). Similar findings are observed in hepatocarcinoma (Huang et al., 2009). In these tumors, the microvascular density measured through endocan immunolabeling (endocan-MVD) correlates more strongly with shortened survival than microvascular density measured through CD34 immunolabeling. Endocan seems to be more a biomarker of endothelial dysfunction whereas CD31, CD34 or von Willebrand factor are widely expressed by all activated and not activated endothelial subtypes. Endocan-MVD was identified in this particular study as an independent prognostic marker for overall survival of hepatocarcinoma patients (Huang et al., 2009).

In conclusion, endocan overpass classical pan-endothelial antibodies such as CD31 or CD34 that are not able to discriminate normal to tumor vessel. Larger series and cohorts of patients are however required to validate endocan immunodetection test as an independent prognostic factor in hypervascular tumors.

Quantifying blood levels of endocan

As endocan is a secreted protein, it can be quantified in blood using a sandwich ELISA method developed with monoclonal antibodies (Bechard et al., 2000). In lung cancer, serum levels of endocan was increased in fifty patients who have not received any therapy (3.34 ng/ml ±0.37) as compared with 25 healthy subjects (0.63 ng/ml ±0.06) (Scherpereel et al., 2003). In this particular series, the highest levels of endocan serum are found in patients with extended forms of cancer (Scherpereel et al., 2003). In a second study with inclusion of 30 patients diagnosed with non small cell lung cancer and with follow ups with a10 month median follow-up, the serum levels of endocan were shown to be inversely correlated with low survival and metastatic spread (Grigoriu et al., 2006). By univariate analysis, overall survival was statistically significantly associated with serum endocan levels, N2 or N3 status, M1 status and tumor stage but not with sex, age, or histologic subtype (adenocarcinoma/ squamous cell carcinoma). The best cut-off level for endocan that differentiated between survivors and nonsurvivors was 1.3 ng/mL and the Cox regression analysis revealed that endocan of inferior 1.3 ng/mL was a significant predictor of overall survival (Grigoriu et al., 2006). High serum endocan levels seem then to be a predictor of bad prognosis in non small cell lung cancers.

The potential of endocan as a prognostic biomarker was also highlighted in a recent study with circulating endocan levels from 3- to 10-fold higher in the sera of clear cell renal carcinoma patients compared to sera from papillary carcinoma patients or from healthy volunteers (Leroy et al., 2010). Moreover, in the clear cell renal carcinoma patients (n = 14), endocan levels were significantly higher in pT3-4 tumor stages (n = 8, median value 6.9 ng/ml) than in pT1-2 stages (n = 6, median value 2.0 ng/ml). However, no significant difference was observed between low (n = 4) and high grade (n = 10) tumors, that could be due of size of the cohort (Leroy et al., 2010).

Taken together, all these recent studies reveal that endocan biomarkers (on tissue sections or by blood sampling) may represent today useful tools to assess endothelial activation and dysfunction in tumors.

Endocan as a companion biomarker?

As we described above, endocan expression is upregulated by VEGF with an increase in levels of mRNA and proteins described both *in vitro* and *in vivo* (Grigoriu et al., 2006; Sarrazin et al., 2006; Maurage et al., 2009). Endocan could therefore be a biomarker of interest in patient follow-ups after surgical treatment (i.e removal of angiogenic tissue) and/or to quantify the impact of an anti-VEGF treatment on vasculature. Grigoriu et al have previously shown *in vitro* that the addition of a blocking anti-VEGF antibody induced a dose-dependent inhibition of VEGF-induced endocan secretion by cultured endothelial cells with an almost complete (95%) inhibition at 0.1 µg/mL (Grigoriu et al., 2006). Abid et al. (2006) have also described that endocan expression in cultured endothelial cells was upregulated by addition of conditioned medium from tumor cells, an effect that was inhibited by the co-addition of neutralizing anti-VEGF antibody (Abid et al., 2006). Endocan was also among the genes identified by a large microarray study as one of the endothelial markers that are significantly decreased under treatment with VEGF receptor-2 kinase inhibitors (Hardwick et al., 2005). Leroy et al. (2010) described recently that addition to cultured endothelial cells of sunitinib abolished the overexpression of endocan induced by VEGF (Leroy et al., 2010). Therefore, endocan release by endothelial cells can clearly be modulated *in vitro* by addition of anti-VEGF compounds. Endocan could then appear to be a pertinent parameter to monitor the tumor response to anti-VEGF targeted therapeutics.

Furthermore, increased systemic levels of endocan has been observed after 2 days of treatment with all-trans retinoic (ATRA) in 17 patients with acute myeloid leukemia (AML) suggesting that ATRA not only affects the AML cells but also endothelial cells (Ryningen et al., 2008). In another study on 22 patients with AML, the same authors compared endocan blood levels in samples collected before and after 7 days of therapy with ATRA. The levels of endocan were significantly increased after treatment when cytokine levels (such as those of FGF-2, CXCL8 and VEGF) did not differ between responder and non-responder patients (Ryningen et al., 2009). In their hands, endocan appears as a pertinent marker reflecting side effect of the ATRA treatments on endothelial component.

This is worth to take in account that endocan blood test as a biomarker will have the following operational characteristics to be readily available source material, with minimally invasive procedure (as a single blood sampling is enough) and with multiple sampling possible without interfering with patient health and quality of life. An endocan blood test could have extended clinical applications for oncologists and other physicians willing to monitor in a personalized therapy approach the response on the vasculature of their patients. An endocan blood test could also allow evaluating treatment efficacy or side effect surrogacy in clinical research or even in new drug development, as endocan level changes may be linked to clinical outcomes.

Conclusions and Perspectives

Biomarkers are by definition molecules used to aid in the pathology diagnosis, stratify patient populations, provide information on disease progression, inform on drug safety and monitor drug efficacy (usually being refers then as companion biomarkers) and help streamline clinical trials.

Endocan immunohistochemical staining is a simple, inexpensive and reliable assay. Since surgery is today one of the most effective methods of treatment of hypervascular cancers, tumor tissue is routinely available for immunohistochemical staining. As tumor microvascular density assessed by endocan detection (endocan-MVD) can be routinely used on tissue sections, endocan could be a pertinent prognosis tissue-biomarker in VEGF-driven cancers to evaluate tumor vascular density and to identify cancer patients that could benefit for anti-angiogenic treatments.

The literature analysis has also revealed endocan test as a promising novel blood-based biomarker that could help in

Tumors	Endocan Expression	Prognosis	Litterature
Breast	Endocan gene expression studies	Higher risk of metastasis	van 't Veer et al., 2002
Lung	Endocan gene expression studies Endocan intratumor immunostaining & high levels of serum endocan	Bad prognosis signature Seems to correlate with metastasis	Borczuk et al., 2004 Grigoriu et al., 2006
Brain	Endocan expression is increased in endothelial cells in high grade glioblastoma	High expression correlate to a shorter survival	Maurage et al., 2009
Ovary	Endocan gene expression studies	Bad prognosis signature	Buckanovich et al., 2007
Kidney	Endocan gene expression studies by microarrays Endocan intratumor immunostaining and increase of circulating level of endocan	Bad prognosis signature Renal clear cell carcinoma of poor prognosis	Amatschek et al., 2004 ; Lenburg et al., 2003, Cifola et al., 2008 Leroy et al., 2010
Liver	Microvascular density measured through endocan immunostaining (endocan-MVD)	Independent prognostic marker for overall survival	Huang et al., 2009

Table 1: Endocan expression in human tumors.

prognosis (Table 1). Today no other molecule is currently available or had made the proof of concept to be a read out of endothelial activation and dysfunction in tumor progression. More validation studies are however still required on larger cohorts on VEGF-driven cancers. Once validated as prognostic biomarkers, endocan could be useful in current practices to identify the cancer patients who will draw benefit from high-cost targeted anti-angiogenic treatments. If validated as a companion biomarker, endocan could furthermore help the clinician to optimize the anti-angiogenic drug dosage and treatment duration. The core capability of personalized medicine using endocan as biomarker – the ability to stratify patients by those likely to respond to treatment (such as anti-angiogenic treatment) or to suffer adverse effects (monitoring vascular integrity)– offers the prospect to optimize the cost /efficacy ratio and quality of care.

Moreover, one can easily imagine that the incorporation of a pertinent tumor endothelial biomarker into a drug development process could also reduce the time, size and cost of clinical trials through the selection of patients who are responding to novel therapies, as well as increasing the chances of regulatory approval of new leads. Finally, the capability to monitor patient response to a targeted treatment through the read out of the vascular integrity can be used to rescue drugs that may benefit specific populations but whose clinical efficacy was missed in unselected populations dominated by non-responders.

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