

## E-selectin: Its Role in Cancer and Potential as a Biomarker

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### Abstract

The involvement of E-selectin in cancer has long been recognized based on histopathological studies, and the important role of E-selectin in cancer progression and metastasis was further reinforced by a number of basic researches. Both the solid state and soluble forms of E-selectin have been tested as a possible biomarker for different cancer types for detection as well as for monitoring. While a number of studies have suggested the potential usefulness of E-selectin as a biomarker, the results from clinical trials are somewhat controversial and it has not been translated into clinical utility. It appears that the use of E-selectin as a single biomarker for diagnosis and prognosis may require more careful evaluation. The utility of E-selectin as a biomarker in conjunction with other biomarkers that are relevant to the biological cascade for E-selectin or are critical for patient prognosis may open up a new venue to further establish E-selectin as a cancer biomarker.

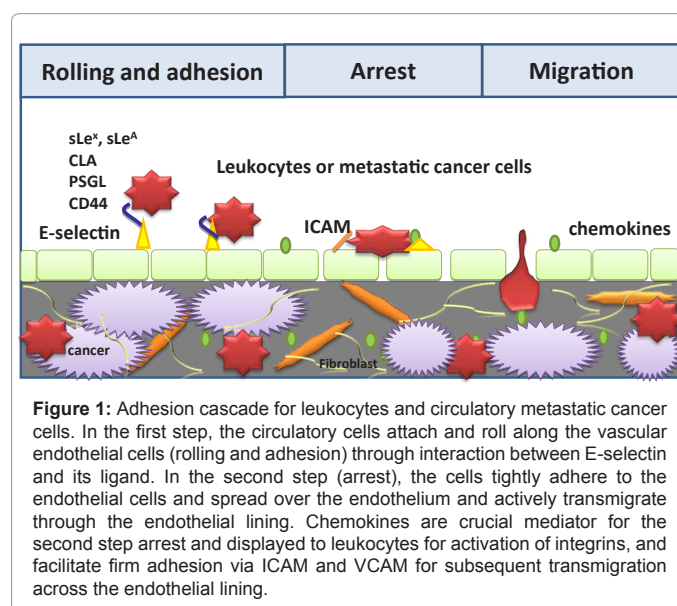
### Biological Role of E-selectin

Selectins are cellular adhesion molecules expressed on the cell surface and assist in cell-cell interaction and adhesion. Selectins (E-, P-, L-selectins) were originally named due to the presence of a lectin domain in the molecule and are a family of three membrane-anchored Ca<sup>2+</sup>-dependent (C-type) lectins that bind to cell-surface carbohydrate ligands and function as adhesion molecules. Their site of expression best classifies the selectins: for example activated endothelium (E-selectin), lymphocytes (L-selectin) and platelets (P-selectin). All selectins consist of a lectin domain at the amino-terminus, followed by an EGF-like domain, a variable number of consensus repeat (CR) domains, a transmembrane portion and end with a short cytoplasmic tail [1]. There is high homology (65%) in the primary sequences among the three selectins throughout the lectin and EGF-like domains, but the CR domains are less conserved.

E-selectin (CD62E, ELAM-1, or LECAM-2) is a highly glycosylated protein that is specifically synthesized by activated endothelial cells. In the very first in vitro experiments reported in 1985, treatment of endothelial cells with cytokines as well as bacterial endotoxins resulted in a dramatic increase in the adhesion of isolated blood neutrophils and led to the identification of E-selectin as a mediator of the adhesion cascade in the inflammation process [2,3]. Later, the major physiological function of vascular E-selectin was defined; specifically, E-selectin recruits leukocytes including monocytes, neutrophils, and lymphocytes to inflamed sites through the interaction with its counter ligands such as sialyl Lewis<sup>x</sup> (sLe<sup>x</sup>), sialyl Lewis<sup>A</sup> (sLe<sup>A</sup>), CD44, Cutaneous lymphocyte-associated antigen (CLA), and P-selectin glycoprotein ligand-1 (PSGL) [4-6] (Figure 1). The interaction of E-selectin with its ligand present on these cells results in a catch bond that switches from rolling adhesion of the circulating cells to firm adhesion by further interactions with other adhesion molecules such as integrins [7]. The lectin domain is responsible for ligand binding and therefore is essential for its to function as an adhesion molecule. E-selectin protein structure is highly conserved among species (73% between mouse and human E-selectins) [8], highlighting a fundamental necessity of this molecule in the process of inflammation in the mammals.

E-selectin expression is absent on normal endothelial cells, but the expression is induced rapidly in response to cytokines such as tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and interleukin (IL)-1 $\beta$ . The E-selectin gene contains binding sites for transcription factors such as NF- $\kappa$ B and AP-1. Therefore in the presence of cytokines, E-selectin transcription, de novo synthesis, and membrane sorting take place within 4 hours [9]. The membrane sorted E-selectin level declines within 24 hours after

the cytokine stimulation due to the internalization and lysosomal degradation [10]. This rapid protein turnover is perhaps necessary to avoid the continuous inflammation, in fact, abundant and continuous infiltration of leukocytes to a tissue leads to chronic inflammatory conditions such as diabetes, atherosclerosis, rheumatoid arthritis and cancer. Thus the two key characteristics of E-selectin expression described as temporal and vessel specific expression have led to substantial interest in the potential exploitation of this protein as a biomarker. In this review, we will summarize literatures and discuss the potential usefulness of E-selectin as a cancer biomarker.



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## The Role of E-selectin in cancer progression and metastasis

Expression of E-selectin on the endothelium is a hallmark of inflammation [9]. Consequently, elevated E-selectin expression on tumor-associated vasculature is observed in many types of cancers including breast [11,12], lung [13,14], prostate cancer [15], and colorectal cancer and pancreatic cancer. For example, the vascular endothelium in metastatic breast carcinoma expresses high level of E-selectin [16,17]. In addition, 68% of prostate tumor patients demonstrated E-selectin overexpression in prostate epithelium and this upregulation was correlated with protein expression level [15]. The expression of E-selectin is induced by stimuli from inflammatory cytokines, in the case of cancer, both cancer cells and tumor stroma can be a producer of cytokines. Breast cancer cells express both TNF- $\alpha$  and IL-1 $\beta$  [18,19], and the expression of such are strongly associated with elevated expression of AP-1 [20], which can activate E-selectin transcription. Therefore, cytokines produced from cancer cells are likely to activate endothelium to recruit immune components at early stage of tumor development. The involvement of E-selectin in the development of tumor stroma has long been recognized as a mediator of the adhesion cascade. As a result of elevated E-selectin expression in cancer, abundant sLe<sup>x</sup> or sLe<sup>A</sup> positive immune infiltrates have also been detected and is associated with metastasis and poor survival in patients with different types of cancer [21,22]. These immune infiltrates are the major component of tumor stroma that assist in cancer cell growth, angiogenesis, invasion through production of an array of cytokines, reactive oxygen species, proteases, angiogenic factors, and growth factors. Among those immune infiltrates, a number of studies demonstrated the pro-tumor role of tumor associated macrophages (TAM) and tumor associated neutrophils (TAN) that are derived from circulatory monocytes or neutrophils, have shown to stimulate tumor growth and metastasis. Both TAMs and TANs express ligands for E-selectins [22] and make the initial contact to the endothelial cells through E-selectin [23-25]. TAMs are a significant component of inflammatory infiltrates in tumor tissue, and high TAM levels are associated with poor patient prognosis and are positively associated with metastasis in many types of cancers (>80%) including breast and prostate cancers [26,27]. TAMs have also been recognized as important producers of growth factors (TGF- $\beta$ , FGF, EGF), pro-angiogenic factors (VEGF, TNF- $\alpha$ , IL-8, MMPs, PDGF), proteases (cathepsin, serine proteases), and cytokines (IL-10), which profoundly affect epithelial cell growth, angiogenesis, local invasion, ECM degradation, metastasis, and immunosuppression [23-25]. Similarly, Tumor-associated neutrophils (TANs) are also abundant in many types of carcinomas and are positively correlated with poor patient prognosis [28,29]. A recent study reported that TGF- $\beta$  stimulates polarization of TANs to acquire a pro-tumor phenotype [30]. Once activated, TANs also become prominent producers of soluble pro-angiogenic factors including VEGF, CXCL-1, and IL-8, and granulocyte-macrophage colony-stimulating factors (GM-CSF and CSF2). Given that both monocytes and neutrophils exploit E-selectin for the initial adhesion to the endothelial surface, it is possible that vascular E-selectin expression may be correlated with an abundance of tumor stroma components as well as its pro-tumor signaling cascade.

In addition to the involvement of E-selectin in inflammation, a flurry of recent evidence has suggested the involvement of E-selectin in the attachment and transmigration of cancer cells including prostate [31], breast [32], colon [33], lung [34], and leukemia [35] through the endothelium [36-38]. Disseminated cancer cells express E-selectin ligands on the cell surface and exploit the E-selectin dependent adhesion mechanism and subsequent tissue migration at distal organs, a process termed as *vasculogenic mimicry* [39] (Figure 1). For example,

metastatic breast cancer cells expressing CD44v4 (one of E-selectin ligands) on the cell surface make the initial contact to the vascular endothelium via E-selectin and transmigrate to the tissue [38]. During this process, the interaction of metastatic cancer cells with endothelial cells *via* E-selectin causes a bi-directional signaling, which causes an increased endothelial permeability through the dissociation of VE-cadherin/ $\beta$ -catenin, in turn, facilitating transendothelial migration of cancer cells [40]. As similar to CD44, overexpression of  $\alpha$ -2,3-sialyltransferase (mediator of sLe<sup>x</sup> synthesis) results in an increase in an E-selectin-dependent transmigration of pancreatic tumor cells [41]. Given the important role of E-selectin and its ligands in tumor progression and metastasis, multiple therapeutic intervention strategies have been developed in an attempt to block the E-selectin mediated adhesion cascade. For example, anti-sLe<sup>x</sup> antibodies significantly inhibited the liver metastases of MKN74 gastric carcinoma cells [42]. A soluble E-selectin fusion protein, which bound to HT-29 colon carcinoma cells, was capable of blocking lung metastases in mice [43]. Furthermore, Cimetidine, a suppressor of E-selectin expression, has shown improved therapeutic outcome in colorectal cancer patients with metastasis from cancer cells that are sLe<sup>x</sup> positive [33]. While a number of studies suggest the involvement of E-selectin in metastasis, the mechanism by which E-selectin mediates the metastasis at distal organs is not fully understood. A recent study addressed this point further by demonstrating that vascular expression of E-selectin at pre-metastatic sites in the lung is induced by vascular endothelial growth factor (VEGF) released from the primary tumor, in turn, facilitating the subsequent adhesion and migration of disseminated cancer cells to the distal target organ [44]. These data collectively accentuate the critical role of E-selectin as a mediator for hematogenous metastasis as well as for tumor progression and further implicate the potential use of E-selectin as a biomarker for early detection of metastasis for certain types of cancer.

## Soluble E-selectin as serum biomarker for cancer detection

The major advantage of E-selectin as a biomarker is an availability of soluble form that sheds from the vessel surface into the blood and makes a non-invasive detection and monitoring feasible. A circulating form of E-selectin (soluble E-selectin or sE-selectin) is detected in the blood as a result of enzymatic cleavage of the external domain or shedding of damaged or activated endothelial cells. sE-selectin has minor effect on the inhibition of leukocyte infiltration, and rather induces monocytes chemotaxis and angiogenesis [45]. Typically, detection of sE-selectin in the blood is performed by conventional ELISA and its detection level is as low as 10 ng/ml. The concentration of sE-selectin appears to correlate with the abundance of E-selectin present on the surface of the cultured endothelial cells [46]. Therefore, abundance of plasma sE-selectin might be an excellent indicator of endothelial activation (i.e., both acute and chronic inflammatory conditions including cancer). Since E-selectin plays an integral role in metastasis, sE-selectin levels can be a useful marker for the management of post-operative patients to monitor the occurrence of metastases. For example, a study showed that the concentration of sE-selectin in serum samples from patients with metastatic breast cancer was significantly higher than the concentration found in a healthy group (33.5 versus 21.8 ng/ml,  $P < 0.01$ ) and in the metastatic breast cancer cohort of patients the levels were higher in patients with liver metastasis than in patients without liver metastasis (55.3 versus 26.0 ng/ml,  $P < 10^{-5}$ ). The increased level of sE-selectin in these patients was associated with reduced overall survival [47]. More recently, the analysis of presurgical sE-selectin levels by ELISA from 78 colorectal cancer patients (40 men, 38 women; mean age, 58+12 years) revealed that sE-selectin levels were

higher in colorectal cancer patients (43 ng/mL) as compared to patients with benign diseases (31 ng/mL), and sE-selectin level was positively correlated with CEA and negatively correlated with patients prognosis ( $P < 0.001$ ) [48]. This study pointed out that a combination of multiple biomarkers may strengthen the prognostic value of sE-selectin. A similar line of evidence suggested that while the use of sE-selectin alone as a marker failed to distinguish lung cancer from benign lung diseases, combining sE-selectin with another biomarker such as Cyfra 21-1; the soluble fragment of cytokeratin 19, resulted in the enhancement of detection sensitivity (99.8%) [49]. All of these studies point to a direction where the sE-selectin might be an excellent serum biomarker for the prediction and detection for certain types of cancer.

## Conclusion

Both soluble and solid states of E-selectin have been investigated as a potential cancer biomarker for early detection, prognosis, and monitoring. However, the results from clinical studies lack consistency and raised a question with regard to feasibility and accuracy of E-selectin as a biomarker. This may be associated with a level of inflammation, which can be influenced by different cancer type, stage, and host immunity. While the involvement of E-selectin in both cancer progression and metastasis is evident, the feasibility of the use of E-selectin as a single biomarker may require more careful evaluation. It seems that sE-selectin can be a good candidate as a serum biomarker when combined with other suitable biomarker/s. Evidently, a combination of biomarkers has led to successful enhancement in the accurate detection of ovarian cancer [50]. Based on the role of E-selectin, a new focus to establish a rational combination of biomarkers for E-selectin and its relevant downstream cascade originating from the tumor stroma maybe warranted.

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