INTERNATIONAL JOURNAL OF
MEDICAL BIOCHEMISTRY

DOI: 10.14744/ijmb.2023.66933
Int J Med Biochem 2023;6(2):117-123

Review

Soluble FMS-like tyrosine kinase-1: An overview

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Abstract

The soluble FMS-like tyrosine kinase-1 (sFLT-1) or soluble vascular endothelial growth factor receptor 1 (VEGF-R1) is a receptor tyrosine kinase which inhibits the mitogenic activity of VEGF by decreasing its availability for binding with transmembrane receptors. VEGFRs exist in various isoforms due to alternative splicing from the same gene. sFLT-1 along with another of its isoform sFLT1-14 is found in abundance in the cytotrophoblast of placenta, and also in the cornea, liver, brain, and kidney. Hypoxia is the key trigger in inducing production of sFLT-1. In normal pregnancy, the soluble receptor regulates the process of vascular transformation by modulating the balance between VEGF-R1 and sFLT-1 activity. Proteinuria and hypertension in pre-eclamptic women have been found to be associated with an elevated level of sFLT-1. sFLT-1 blocks the podocyte-derived VEGF and induces damage of the glomerular endothelium leading to proteinuria and blockage of endothelial nitric oxide signaling pathways resulting in hypertension. In ectopic pregnancy, the abnormal implantation of the embryo simulates a hypoxic environment inducing excess production of VEGF and its consequent binding to sFLT-1. The usage of sFLT-1 as an early biomarker of preeclampsia, ectopic pregnancy, and other failing pregnancies is being studied. Variation in sFLT-1 levels has also been identified in cardiovascular diseases, chronic kidney disease, non-healing ulcers, and liver cirrhosis to name a few. Therapeutic use of sFLT-1 to reduce angiogenesis in various conditions like cancer is currently being pursued.

Keywords: Angiogenesis, ectopic pregnancy, hypoxia, pre-eclampsia, VEGF

How to cite this article: Selvarajan S, Ramalingam J, Venugopal V. Soluble FMS-like tyrosine kinase-1: An overview. Int J Med Biochem 2023; 6(2):117-123.

Soluble FMS-like tyrosine kinase-1(sFLT-1) is the soluble variant of the Vascular Endothelial Growth Factor (VEGF) receptor-1, a protein tyrosine-kinase with anti-angiogenic characteristics. It was first discovered by Kendall and Thomas in 1993 [1]. VEGF is a physiological regulator of angiogenesis in the skeleton, growth of the embryo, and also involved in vasculogenesis, angiogenesis, and lymphangiogenesis during embryonic and postnatal development in reproduction [2].

sFLT-1 binds both PlGF and VEGF, thereby reducing their concentration in free form and inhibiting angiogenesis. It is therefore an important regulatory component of angiogenesis in various tissues within the body and implicated in numerous disease conditions with abnormal vascular growth.

sFLT-1 Structure

Kendall et al. [1] determined that alternative splicing of VEGF pre-mRNA produces two diverse products (Fig. 1):

VEGF-R1/ FLT-1 is the complete-length membrane-traversing receptor that facilitates VEGF mitogenic action promoting angiogenesis and sFLT-1 is a truncated soluble form of VEGF-R1 without the transmembrane domain and consequent absence of mitogenic activity.

sFLT-1 has a unique 31 amino acid sequence on the C terminal which is different from VEGF-R1. The latter has additional transmembrane and intracellular domains responsible for its VEGF binding activity. sFLT-1 also has a six N-terminal im-

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Submitted: January 02, 2023 **Revised:** January 21, 2023 **Accepted:** January 22, 2023 **Available Online:** March 09, 2023

munoglobulin-like domain along with a site for binding PlGF and VEGF on the second domain from the N terminal [1]. There is a binding site for heparin made of ten basic amino acids in the third domain from the N terminal. The pI of sFLT-1 is 9.51, so at physiological status, it has a positive charge [3].

Isoforms of sFLT-1

According to the UniProt database, there are eight isoforms of the VEGF receptor 1 [4]. The VEGFR-1, sVEGFR-1(sFLT-1), and sFlt1-14 relate to isoforms 1, 2, and 3, respectively. Isoform 4 is additionally another extracellular soluble protein, smaller than sFlt1-14 and sVEGFR-1, and formed by proteolytic cleavage. Isoforms 5 to 8 are linked to the intracellular area of this receptor. Isoform 5 encompasses the entire tyrosine kinase area, while isoforms 6, 7, and 8 are truncated forms lacking various N-terminal regions of the tyrosine kinase domain. The biological significance of isoforms 4 to 8 is at present unknown.

sFLT-1 Gene and mRNA Expression

The gene for sFLT-1 is positioned on chromosome 13q12.3, which is the long (q) arm of chromosome 13 at the position of 12.3. Holt et al. [5] identified a unique endogenous factor, Raver2, which furthers the production of sFLT-1. They localized Raver2 and PTB FLT pre-mRNA and evidenced that Raver2 enhances PTB's link with FLT-1 pre-mRNA. They suggest that this promotes a specific type of RNA processing called intronic polyA activation resulting in production of the soluble variant of the receptor.

The same gene is responsible for the production of VEGFR1 and sFLT-1-alternative splicing of the mRNA leads to production of the two different receptor subtypes. The sequence 3' of the sFLT mRNA splice site (GUGAGC) nevertheless looks like an unprocessed donor site (GURAGU). The mRNA coding region distinctive to this cDNA has been confirmed to be present in vascular endothelial cells. Thus, sFLT mRNA arises from the absence of processing this potential splice site resulting in a direct read-through of the contiguous intron sequence that can alternatively be removed to generate mRNA encoding the mitogenically functional membrane-spanning FLT receptor.

Similar splice-site skipping of 3′ introns accounts for the generation of mRNAs that encode soluble forms of several other proteins including immunoglobulin heavy chains, interleukin-5 (IL-5) receptor A subunits, and FGF receptors [6]. The competitive processing of alternative polyadenylylation sequences represents a general mechanism for generating soluble forms of membrane- bound receptors, regulating their expression and consequently modulating the biological responses mediated by these genes. An AATAAA polyadenylylation consensus signal sequence identified in the 3′ non-coding region near the end of the 2.6-kb sFLT cDNA clone could, in part, regulate the FLT/sFLT switch [1].

Regulation of Gene Expression

Hypoxia is the trigger which releases copious amounts of sFLT-1 from monocytes or macrophages. This process is stimulated by granulocyte-macrophage colony-stimu-

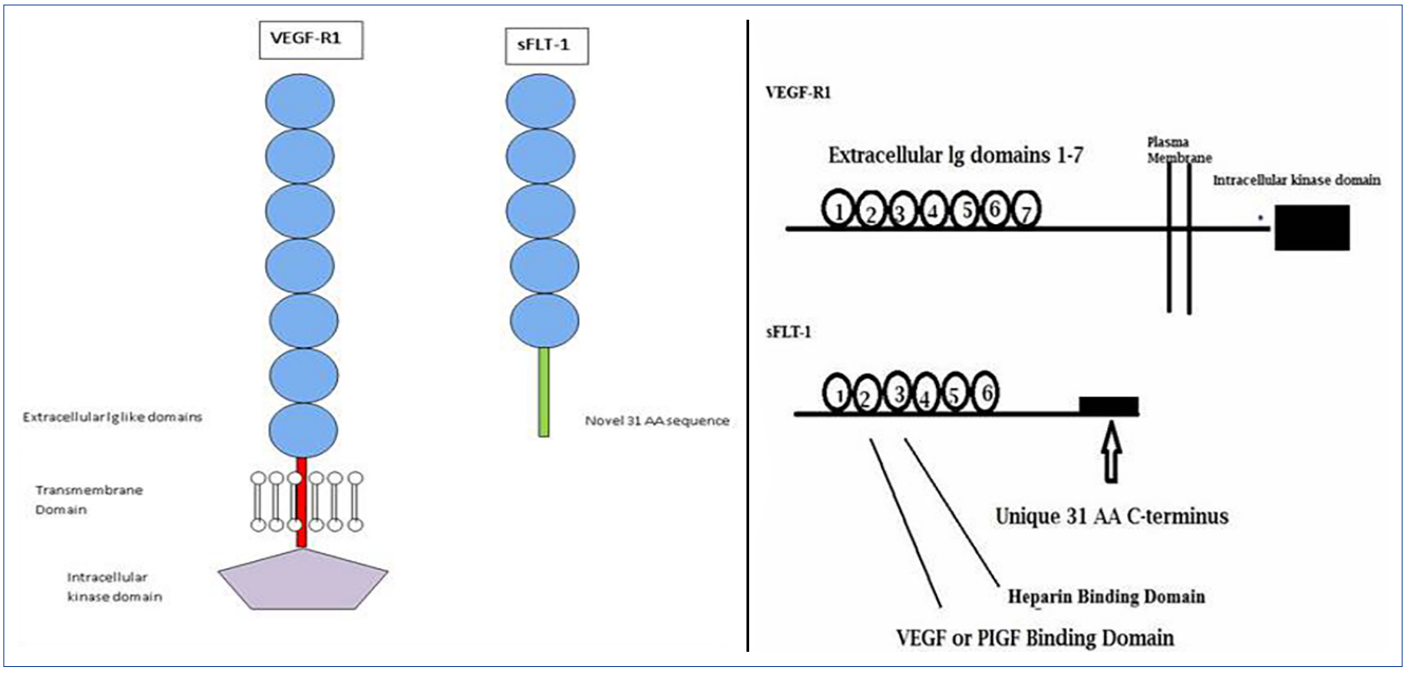

Figure 1. Structure of sFLT-1 and its binding sites.

VEGF-R1 FLT-1 is the complete-length membrane-traversing receptor that facilitates VEGF mitogenic action promoting angiogenesis and sFLT-1 is a truncated soluble form of VEGF-R1 without the transmembrane domain and consequent absence of mitogenic activit. VEGF-R1: Vascular Endothelial Growth Factor receptor-1; sFLT-1: Soluble FMS-like tyrosine kinase-1.

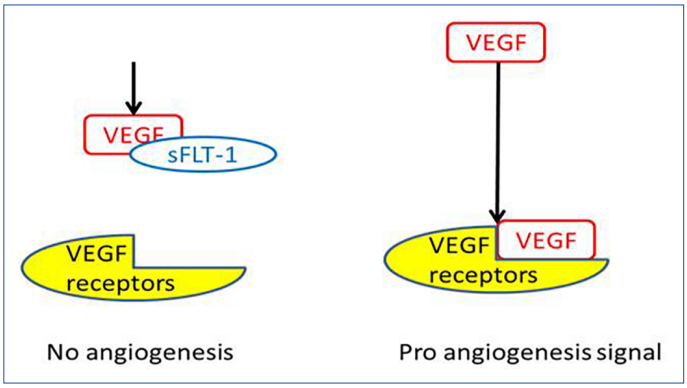

Figure 2. Action of sFLT-1 on VEGF and its receptor.

sFLT-1 binds VEGF inhibiting its mitogenic activity (Figure 2) on endothelial cells and negatively regulates angiogenesis in various tissues like the liver, brain and kidney. VEGF: Vascular Endothelial Growth Factor; sFLT-1: Soluble FMS-like tyrosine kinase-1.

lating factor and is also dependent on hypoxia inducible factor (HIF)-2α [7]. Two other cytokines, namely, IL-4 in macrophages and IL-6 in endothelial cells were found to increase the production of both the soluble forms. Geifman et al. [8] identified another signaling pathway indicating that hypoxia increased production of sFLT-1 involving activation of growth arrest, Gadd45a factor which causes DNA damage and also p38 phosphorylation.

Both VEGF-R1 and sFLT-1 are produced in endothelial cells while in non-endothelial cells especially the placenta, mainly the soluble forms, namely, sFLT-1 and sFlt1-14 are produced. Within the cytotrophoblasts of the placenta, an exposure to hypoxia results in production of both the soluble isoforms probably due to stabilization of HIF-1α [7]. Drugs such as ouabain, a cardiac glycoside, aspirin, and metformin decrease the production of the soluble forms in the cytotrophoblast [9]. Phorbol myristic acid is an activator of protein kinase C which increases the production of sFL-1 mRNA and the protein itself in endothelial cells [10]. Most importantly, the accumulation of VEGF-A can also stimulate the production of sFLT-1.

Physiological Roles of sFLT-1

Since sFLT-1 does not have the transmembrane domain, it is not bound to the cell membrane and therefore, is free to circulate in the bloodstream from the site where it is secreted to the other sites where its action is exerted. sFLT-1 binds VEGF inhibiting its mitogenic activity (Fig. 2) on endothelial cells and negatively regulates angiogenesis in various tissues such as the liver, brain, and kidney. A necessary requisite for angiogenesis is destabilization of pericyte-endothelial cell interaction and an alteration in the perivascular cytoskeleton and modification of adhesions with the basement membrane. This is effected by the soluble receptor which shifts α5β1 integrin signaling from a classical adhesion pathway to a more dynamic one [4].

Inhibition of VEGF function in vivo by sFLT could promote quiescence in confluent endothelial-cell monolayers, act as a feedback mechanism to terminate angiogenesis and vascular permeability, and prevent blood vessel growth into normally avascular tissues, such as cornea and hyaline cartilage. Eslani et al. [11] stated that sFlt-1 is expressed in the eye to maintain avascularity in the cornea.

sFLT-1 In Normal Pregnancy

Although small quantities of sFLT-1 are secreted by the monocytes and endothelial cells, in pregnancy, the placenta remains the major source [7]. sFLT-1 mRNA is strongly expressed in placenta and levels in serum decrease appreciably post-delivery of placenta.

A crucial aspect of successful implantation of the zygote within the uterine endometrium is the establishment of angiogenesis – the physiological process of growth of new blood vessels from previously existing microvasculature involved in growth and repair.

In normal pregnancy, enormous quantities of VEGF are secreted by the macrophages at the Nitabuch's stria of decidua during the first trimester of pregnancy [12]. This is where the process of vascular transformation is necessitated instead of angiogenesis. A balance between angiogenesis and vascular transformation is therefore necessary. Therefore, sFLT-1 may be involved in neutralizing the influence of VEGF on maternal endothelial cells in the decidua. In a research conducted by us in normal pregnant women, sFLT-1 levels were observed to be directly correlated to the gestational age, and increased with gestational age in early pregnancy [13]. A linear regression equation for predicting the sFLT-1 level based on the gestational age=282.57+94.23* (gestational age in weeks) was obtained in this study.

During placentogenesis, the extravillous cytotrophoblasts which are a unique type of fetal cells invade the uterine spiral arteries. Due to this invasion, the epithelium of these arteries become more permeable to accommodate the augmented requirement of blood circulation during pregnancy. To achieve this, there is a decrease in adhesion molecules of the epithelium and an increase in those of the endothelium occurs which is called pseudovasculogenesis. sFLT-1 mRNA is produced by the villous trophoblast in substantial amounts all through pregnancy [12]. Since there is a dramatic increase in the size of the placenta and in consequence that of the villous trophoblast in the course of pregnancy, it is to be expected that the overall sFLT-1 production will increase.

sFLT-1 is produced by the trophoblastic cells of the placenta which are positioned between the mother's blood vessels on one side and the umbilical vessels on the side of the fetus [14]. Thereby advocating that sFLT-1 traps and binds VEGF and PlGF forming a barricade in opposition to atypical vascular penetrability and aberrant angiogenesis, for instance the merging of foetal blood vessels to maternal capillaries. The trophoblastic villi have an uninterrupted communication with maternal circulation within the placenta and therefore, the proteins produced there can be identified in maternal blood.

The study by Lam et al. [14] in 2003 evaluated the roles of VEGF and its receptors in human embryo implantation. The results suggest that VEGF may be the essential angiogenic factor responsible for the implantation of human pregnancy and it may be a potential target for the treatment of EP. It has been demonstrated in animal models that VEGF plays a crucial role in pregnancy. Inhibition of VEGF action can completely block the implantation [2] or lead to embryonic lethality.

In the serum samples from non-pregnant women and males, no significant sflt-1 activity could be detected. Even if additional tissues produce sflt-1, their contribution to serum levels, at least in normal subjects, is significantly lower than that seen during pregnancy [15].

In a study by Wathén et al. [16], decreases in the levels of sFLT-1 post a cesarean section were measured and they found the curve to be biphasic. According to their calculation, the half-life was similar to total β-hCG which is roughly about 24–46 h. Typical of proteins, the elimination occurs in two phases: An initial rapid clearance probably from the intravascular space and a slower one possibly from the extravascular space. The route of elimination is unknown, but based on its molecular size, 110 kDa [1], it is likely to be mainly removed by the liver and/or the reticuloendothelial system.

sFLT-1 In Pathological Conditions (Table 1)

Large amounts of sFLT-1 were found in the fluid of non-healing wounds and chronic ulcers [17]. Increased plasma levels are noticed in patients with cardiovascular diseases, heart failure, and chronic kidney disease [18]. Its isoforms are observed in varying stages of inflammation and may be deemed a marker of sepsis [19]. Acute pancreatitis and liver cirrhosis are other conditions with increased levels of sFLT-1. It is also being studied as a marker of atherosclerosis [20].

The findings from a familial high-risk for psychosis study demonstrated that sFLT-1 can predict longitudinal clinical and brain structural changes. Furthermore, their findings further support the hypothesis of altered microvascular circulation in schizophrenia and those at risk [21]. A study by Harris et al. [22] implicates this tyrosine protein kinase in Alzheimer's disease. Due to its importance in normal growth and development of the fetus, its role in abnormal and failing pregnancies has been greatly studied.

sFLT-1 in Abnormal Pregnancies

sFLT-1 has been found to regulate not only the physiological but also the pathological vascular changes in the female reproductive tract. Habeeb et al. [23] stated that an abundance of sFLT-1 was seen in parallel to a poor response to gonadotropins in ovarian stimulation protocols. Independent of the cause of an early pregnancy failure, the premature, and excessive entry of maternal blood inside the placenta has two effects on the villous tissue. First, a direct mechanical effect with most of the villi becoming progressively embedded inside large intervillous blood thrombi and secondly an indirect widespread O_2-mediated effect causing oxidative damage leading to major apoptosis and necrosis of the villous trophoblast [24]. Overall, the consequences are placental degeneration with complete loss of syncytiotrophoblast function and detachment of the placenta from the uterine wall. This mechanism is common to all miscarriages irrespective of the time at which it occurs in the first trimester depending on the etiology.

Table 1: sFLt-1 in various clinical conditions

sFlt-1 in pathological conditions
Non healing wounds and chronic ulcers
Cardiovascular disease
Heart failure
Chronic kidney disease
Alzheimer's disease
Schizophrenia
Acute pancreatitis
Liver cirrhosis
sFlt-1 in abnormal pregnancies
Miscarriages
Failing pregnancies
Pre-eclampsia
Ectopic pregnancy
sFlt-1 as a therapeutic agent
In Tumor metastasis
Diabetic retinopathy
Age-related macular degeneration
Diabetic nephropathy

sFLT-1: Soluble FMS-like tyrosine kinase-1

Yousif et al. [25] showed that O_2 concentration in the placental bed blood is inversely related to sFlt-1 in early pregnancy. A decreased level of sFlt-1 in maternal serum before a complete miscarriage suggests that impaired placentation may be associated with placental metabolic changes before the appearance of clinical symptoms of miscarriage and these changes are modulated by an abnormal increase in O_2 concentration inside the placenta after implantation.

sFLT-1 in Pre-Eclampsia (PE)

In 2003–2004, numerous investigators stated that an uncharacteristic raise in the level of serum sFlt-1 in expectant mothers is associated with the degree of PE [26]. Furthermore, adenoviral transfer of the sFLT-1 gene to pregnant rats has shown to cause a disorder similar to PE [20]. The ratio of sFLT-1 to PlGF was found to be increased in pre-eclamptic women in numerous studies [27]. sFLT-1 released from the placenta travels in the mother's circulation to distant target organs and may be responsible for the multisystem endothelial dysfunction in PE [28].

The two major symptoms of preeclampsia are hypertension and proteinuria. Hypertension and proteinuria are also the most common adverse effects encountered in cancer patients treated with VEGF-neutralizing antibody [29]. Artificial expression of sFlt-1 using a vector in a pregnant rat model induced hypertension and proteinuria [30]. These facts strongly suggest that sFlt-1 overexpression in PE is a crucial cause of its symptoms.

Podocytes in the glomeruli of the kidney secrete VEGF at physiological levels and maintain the glomerular endothelial cells in a healthy state, producing urine without leakage of serum proteins. Suppression of VEGF secretion from podocytes results in severe proteinuria [31]. Thus overexpression of the VEGF-trapping molecule sFLT-1 may block podocyte-derived VEGF and induce glomerular endothelial damage resulting in proteinuria in PE. It can also affect the development of various kidney diseases such as diabetic nephropathy, lupus nephritis, renal transplant, and chronic kidney disease [31].

VEGF signals stimulate eNOS and increase the production of NO, a vasodilator in endothelial cells. Furthermore, VEGF is a strong vascular permeability factor. Thus, a decrease in both NO and permeability through VEGF trapping by sFLT-1 may cause hypertension. Blocking NO signaling was found to increase serum sFLT-1 in a rat model of PE [32].

Expression of VEGF receptors is found to be up regulated by hypoxia by a HIF-1 dependent mechanism. Given that trophoblasts are the main source of sFLT-1 in PE, viral or bacterial infection, or abnormal stress, such as hypoxia in the placenta, may induce these cells to overexpress sFLT-1 [33]. An sFLT-1 blocking agent that is safer to both fetus and mother can be a useful tool to control PE.

Beside the short-term regulation by hypoxia and NO levels, genetic variation also influences sFLT-1 levels. Women with a history of PE showed increasing sFLT-1 up to 18 months postpartum, advocating a genetic basis [34].

Interestingly, increased sFLT-1 was detected as early as 5 weeks before onset of symptoms in preeclamptic women which means it can be used as a marker of the disease [35]. In another study, variation in sFLT-1 was noticed only in early onset PE whereas the late onset disease showed only a small decrease in PlGF [36]. Nevertheless, elevated sFLT-1 was also found to be related to non-preeclampsic intra-uterine growth retardation of fetus, curbing its utility as a biomarker for PE [37]. Muller et al. [38] state that the sensitivity and specificity of sFLT-1 were too less to aid in prediction of PE.

The gene for sFLT-1 is located on chromosome 13q12; the correlation of fetal trisomy-13 with increasing rates of PE could be due to the extra copy of the gene. Primiparous women have higher baseline sFLT-1 which could cause the higher incidence of PE among them [39].

sFLT-1 in EP

Since the implantation of the EP at the tubal site is unfavorable, it provides an abnormal environment with insufficient nutrition and oxygen to the developing embryo. This hypoxic environment increases the expression of VEGF in the ectopic site. This pro-angiogenic growth factor and its receptors were increased in production in EP [40]. It has been identified that VEGF in serum of women with EP is elevated in comparison with intrauterine pregnancy [40]. There is also a reduction in the levels of sFLT-1 in EP women, but the exact mechanism behind the decline in sFLT-1 is unclear. It may be either due to the binding of sFLT-1 receptor to the excessively expressed VEGF or a decrease in sFLT-1 production or both. Measurement of sFLT-1 therefore aids in identifying implantation of the embryo at an ectopic site and can therefore be used as a biomarker for EP.

Daponte et al. [41] suggest that a combined measurement of sflt-1 along with PlGF or a ratio of the two can aid in the diagnosis of an EP and differentiate it from missed abortion. The genetic expression of the above said that markers were found to be impaired in the trophoblastic cells of pregnant women with EP and missed abortion. Martínez-Ruiz et al. [42] state that in a comparison study of PlGF, sflt-1 and progesterone as markers for EP, sflt-1 had the highest potential to diagnose an EP and also to differentiate it from a missed abortion with a sensitivity of 84.5% and specificity of 86.3% . They proposed a cutoff value of <93 pg/mL, to differentiate between ectopic pregnancy and abnormal IUP. They also suggest that a combination of sflt-1 with progesterone may improve the diagnostic accuracy. In a research study on this novel biomarker conducted by us, the median sFLT-1 level in EP was 419 pg/ml which was significantly lower than that in normal pregnancy (898 pg/mL). Receiver operating characteristic curve analysis in our study showed that at a cutoff of 623 pg/mL, sFLT-1 was able to distinguish an EP from a normal intrauterine pregnancy with a sensitivity of 98.6% and a specificity of 90.7% [12].

sFLT-1 as a Therapeutic Agent

Since disease-related neovascularization, such as tumor angiogenesis, is mediated by VEGF, exogenous sFLT could be a therapeutically useful agent for specifically and efficiently inhibiting pathological blood vessel growth and, perhaps, blood-borne tumor metastasis [43].

Anti-VEGF drugs are used along with laser ablation to treat patients with diabetic retinopathy. These drugs have short half-lives in the vitreous of the eye resulting in the need for frequent intravitreal injections. To improve the intravitreal half-life of anti-VEGF drugs, such as the VEGF decoy receptor sFlt-1, multivalent bioconjugates of sFlt-1 grafted to linear hyaluronic acid chains termed mvsFlt are being studied [44]. It is also being currently tested in the treatment of age-related macular degeneration [45].

Bus et al. [46] report that normalizing VEGF-A levels with sFLT-1 might be a viable approach for treating individuals with existing diabetic nephropathy by reducing endothelial activation, glomerular macrophage infiltration, and glomerular inflammation, thereby reversing kidney damage.

Conclusion

The role of sFLT-1 in pathological angiogenesis has gained importance due to its action as a VEGF sink and may also be due to the inhibition of VEGFR-1 dimerization and signaling. Hypoxic signaling regulates the expression of this soluble receptor, and due to the absence of a transmembrane domain, it is carried in circulation to exert effects on various target organs such as heart, liver, brain, and kidney. The main source of sFLT-1 in pregnancy is the placenta and plays a major role in establishment of a balance between angiogenesis and vascular transformation. The interaction of sFLT-1 and its other isoform sFLT1-14 and their role in the regulation of angiogenesis is being studied to develop new therapeutic strategies to target these receptors in various diseases.

Conflict of Interest: The authors declare that there is no conflict of interest in this study.

Financial Disclosure: The authors acknowledge the Indian Council of Medical Research (ICMR), New Delhi for providing financial assistance in the form of the TSS fellowship number PhD (Integrated)-30-F.T./I/2014.

Peer-review: Externally peer-reviewed.

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