Impact of *SULF1* Gene on Angiogenesis

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Abstract

Single-gene disorders occur when mutation in a gene causing alteration of gene function; while in multifactorial disorders, mutations occur in multiple genes, and these are usually coupled with environmental causes. In addition, in a multifactorial disorder such as diabetes, the complication is under the influence of different genes. For example, in diabetic retinopathy many genes are involved including genes related to angiogenesis. One of these genes is *SULF1*. Studying the function and molecular bases of the mutations in these genes plays an important role in understanding the pathology of diseases and is helpful in management, treatment and even prevention of them.

It has been identified that *SULF1* can interfere in signaling of many heparan binding growth factors and morphogens. Heparan sulfate (HS) proteoglycans are glycoproteins which regulate many signaling pathways. HS is added to proteins during Golgi modifications. Sulfatase 1 is a catalytic enzyme which removes sulfate groups from HS of proteoglycans. The angiogenesis-related studied molecules which can be regulated by heparan sulfate including VEGF, FGF, Wnt, BMP, HGF, HB-EGF and SHH. In this review, we have focused on the role of these signaling molecules on angiogenesis and the role of *SULF1* in their regulation.

Keywords: Angiogenesis, *SULF1* gene, Heparan sulfate, Sulfatase1 enzyme

Introduction

Heparan sulfate (HS) proteoglycans are glycoproteins containing heparan sulfate groups (1, 2), which are anchor site for a broad variety of signaling proteins and regulate many signaling pathways and functions (3). During post-translational modification, Golgi apparatus adds heparan sulfate units to proteins (4), which is essential for normal embryonic development and play crucial role in regulating key developmental signaling pathways. This requirement is due to the obligatory role for HS in signaling pathway of many growth factors and morphogens that bind to sulfated domain in the HS polymer chain. The sulfation patterning of HS is determined by a complex of sulfotransferases and endosulfatases that transfer and remove 6-O-sulfate of the HS (5, 6).

Before the identification of quail orthologous of *SULF1*, heparan sulfatases considered unchanged during life. The discovery showed

that alteration of heparan sulfate binding affinity to signaling molecules is due to the change in binding sites of heparan sulfate groups. *SULF1* is homologous with lysosomal N-acetyl glucosamine sulfatases (G6-sulfatases), which catalyze the hydrolysis of 6-O-sulfates from N-acetyl glucosamines of heparan sulfate during the degradation of HSPGs. In contrast to its lysosomal homolog, the enzyme is located in cell surface and is active in neutral PH (7). Shortly, orthologs of *QSULF1* were found in human and murine and named *HSULF1* and *MSULF1*, respectively. The paralog of *HSULF1*, called *HSULF2* was identified with 63% to 65% homology to *HSULF1*(8).

HSULF1 is located on chromosome 8 and produces a 871-amino acid protein, while *HSULF2* is located on chromosome 20 and its protein is comprised of 870 amino acids. Both of these genes are members of arylsulfatases family and very similar to arylsulfatase A (ARSA) and B (ARSB), and glucose amine 6-sulfatase (9, 10). A highly conserved residue in prokaryotic and eukaryotic sulfatases is a cysteine residue, which is post-translationally modified to N-formyl-glycine. Its hydroxylation by a water molecule to form a hydroxyl-formyl-glycine is a necessary step for sulfatases enzyme activity (11). *QSULF1* is reported to be asparagine glycosylated and this N-linked glycosylation has been shown to be necessary for its heparan binding and its 6-O-desulfation activity (12). *SULFs* contain a hydrophilic domain (HD) of about 320 amino acid residues, which is required for enzymatic activity and acts as a high affinity heparin/haparan sulfate interaction domain (13). HD of *SULF1* and *SULF2* are associated with the cell membrane component through electroacotatic and thereby modulating growth factor signaling (14).

In this review, we briefly discuss the role of *SULF1* in the cancer pathogenesis and then in more details focus on the role of signaling molecules regulated by heparan sulfate (VEGF, FGF, Wnt, BMP, HGF, HB-EGF and SHH) on angiogenesis and the role of *SULF1* in regulating them.

Cancer Pathogenesis and *SULF1*

Due to the role of *SULF1* in the signaling of growth factors and morphogens, it is quite predicable to observe important roles for it in molecular pathogenesis of different diseases. The most studied diseases are cancers. The role of *SULF1* has been emphasized in several cancers, due to its interference in different invasive characteristics of cancers. First signs of *SULF1* contribution to cancers were observed in ovarian cancer, in which it was down-regulated, indicated to be due to enhanced EGFR/ERK signaling (15). *SULF1* dysregulation continued to be understood in different cancers. Down-regulation of *SULF1* was observed in breast cancer, which was indicated to be due to FGF2, VEGF165 and hb-EGF enhanced signaling through their receptors, interfering in part in breast cancer angiogenesis (16,17). Down-regulation of *SULF1* in hepatocellular carcinoma cell lines were observed too. The role of *SULF1* in hepatocellular carcinoma cell line is believed to be through interfering FGF and HGF signaling, and also it is shown that overexpression of *SULF1* can enhance acetylation of H4 and inhibiting histone deacetylase (HDAC), which leads to inhibition of MAPK and AKT pathways (18, 19). *SULF1* expression in pancreatic cancer was not uniformly absent. Inconsistently with ovarian and hepatocellular carcinoma, *SULF1* expression in an *SULF1* negative Panc-1 cell line, only inhibited FGF2 signaling, which suggests a cell specific manner of *SULF1* (20). Interestingly, pancreatic cancer in early stages have higher sulfated HSPGs; but during metastasis it reduces significantly (21). Enhanced expression of *SULF1* reduces in myeloma cells, which triggers FGF-2 signaling (22). Head and neck squamous cell carcinoma is another cancer in which several cell lines show reduced *SULF1*, effect of which seems to be through FGF-2 and HGF signaling (23).

VEGF and *SULF1*

Vascular endothelial growth factor (VEGF) family is a well-known angiogenic family containing 6 known members, namely, VEGFA, VEGFB, VEGFC, VEGFD, PIGF and VEGFF, acting through three receptors VEGFR 1, 2 and 3. VEGFA plays the most important role in angiogenesis and VEGFR2 is the main receptor for angiogenic and mitogenic signaling in endothelial cells (24). VEGFA is a homodimeric heparan binding protein, and VEGF165 is the main heparan binding variant (25). VEGF triggers a wide variety of cell signaling pathways to promote angiogenesis through activating AKT/PKB, P38, FAK and paxilin and raf-MEK-ERK to enhance cell survival and vascular cell permeability, reorganize actin, focal adhesion turn over and increase cell proliferation (26-28).

In 2006, Narita et al. showed that *SULF1* knockdown enhanced HUVECs proliferation through increasing VEGF165 signaling (29). Consistently, another study in 2006 by Uchimura showed that SULFs decreases VEGF binding to heparan sulfates, hence inducing VEGF signaling (30). VEGF creates new blood vessels during embryonic development and injuries but dysregulation in VEGF signaling causes many cancers such as lung and breast cancers and angiogenesis related diseases including diabetic retinopathy, psoriasis and rheumatoid arthritis (31-34).

FGF and *SULF1*

Fibroblast growth factor (FGF) family members bind to heparin and possess broad mitogenic and angiogenic activities. FGF2 is the main protein implicated in diverse biological processes. FGFs regulate many developmental processes including brain patterning, branching morphogenesis and limb development. Dysregulation in these signaling pathways causes angiogenesis related diseases such as rheumatoid arthritis, psoriasis, diabetic retinopathy and many cancer e.g. breast cancer (35-39). By binding to FGFR, bFGF promotes cell signaling through RAS, MAP kinase, Erk, Crk, JNK and PKC pathways to proliferate endothelial cells, promote their migration and enhance angiogenesis.

Jin-Ping Lai et al. in 2004 revealed that down-regulation of h*SULF1* enhanced FGF signaling in hepatocellular carcinoma (40). Consistently, in 2005 another study on pancreatic cancer cells showed that overexpression of h*SULF1* interfered FGF2 signaling (41). These results were repeated for FGF2 in mesenchymal cells of quail and xenopus (29,42-44). In 2010 Otsuki et al. showed that articular cartilage of *SULF1* and SULF2 -/- mice has enhanced FGF/ERK pathway (45). Sulfatases-modifying factor 1 (SUMF1) activates *SULF1* and SULF2. Buono et al, in a study in 2010 revealed that SUMF1 -/- hematopoetic stem cell progenitor gain constitutively activated FGF signaling (46).

Wnt and *SULF1*

Wnt family is comprised of 19 Wnt secreting glycoprotein, acting mainly through 10 known fzd transmembrane receptors. The family members trigger two signaling modes: canonical signaling which is through fzd receptors and is also called Wnt/β catenin pathway, and non-canonical signaling consisting of Wnt/Ca^{2+} and planar cell polarity (PCP) pathways, which triggers fzd receptors, receptor tyrosin kinase-like orphan receptor (Ror) family and receptor-like tyrosin kinases (47,48). Endothelial cells express different Wnt proteins and receptors including Wnt5a, Wnt7a, Wnt10b, fzd1, fzd2, fzd4, fzd5, fzd6, fzd7, fzd9, fzd10, Lrp5, Lrp6 and ryk (49-53). Wnt also induces several angiogenic genes namely VEGF, FGF, IL-8, MMPs and endothelin (53-59). Studies on knockout mice and genetic diseases have introduced several members of the family interfering the angiogenesis including Wnt2, Wnt4, Wnt7b, fzd4 and fzd-5 (60,61). Wnt signaling is essential for embryonic development and homeostatic self-renewal in adult, while its dysregulation in Wnt signaling causes many diseases such as colon cancer, leukemia,

rheumatoid arthritis, diabetic retinopathy and psoriasis (62-64).

In 2001, Dhoot et al. revealed the first evidence on *SULF1* role in signal transduction by mutating the catalytically cysteine to alanine to prevent formyl-glycine formation. They showed that *SULF1* is responsible for Wnt release from heparan sulfates (7). Consistently, enhanced Wnt signaling was observed in pancreatic adenocarcinoma, hepatocellular carcinoma and odontoblast cell lines. In addition, hs6st and *SULF1* nulls differentially elevate both Wnt (Wingless; Wg) and BMP (Glass Bottom Boat; Gbb) ligand abundance in the synaptomatrix. Similar results were reported for xenopus *SULF1* (xt*SULF1*)(65-69); while in 2011, Jie Li et al reported that *SULF1* inhibits Wnt/β catenin signaling in gastric cancer cell line MKN 28. They also reported no effect on Wnt signaling in AGS cell line, considered to be due to G34E mutant allele in CTNNB1, which constitutively activates wnt/β catenin signaling pathway independent of Wnt (70). Sahota et al. showed that the novel shorter variant of *SULF1*, variant B, in contrast to *SULF1*A inhibits Wnt signaling and promotes angiogenesis (71). These controversial results suggest that *SULF1* impact on Wnt signaling might be cell-specific.

BMP and *SULF1*

Bone morphogenetic protein (BMP) is a unique sub-family of TGF-β super family with low molecular weight (72). It is divided into three subgroups: 1: BMP2 and BMP4 (BMP2/3 subgroup), 2: BMP5, BMP6, BMP7, BMP8 and drosophila Gbb (BMP7 subgroup) and 3: GDF5, GDF6 and GDF7 (GDF5 subgroup). BMPs have shown to have both pro-angiogenic and anti-angiogenic activity. BMP 2 and BMP4 have shown to have pro-angiogenic activity through interaction with ALK3/6 and BMPRII and activation of SMAD 1/5/8, as well as BMP6, 7, and GDF5 by interaction with BMPRII, ALK2/3/6, ACTIIA and ACTIIB. Moreover, it is shown that BMP2, 4, 6 and 7 up-regulate VEGFA (20,21). On the other hand, BMP9 and BMP10 have anti-angiogenic function by triggering BMPRII, AKL3/6 and ACTRIIA to activate SMAD1/5/8. BMP9 is shown to inhibit VEGFA expression (73). The activity of BMPs is known to be regulated by their inhibitors noggin and chordin(74).There are several reports on noggin impact on angiogenesis, as negative regulator of developmental angiogenesis through inhibition of BMP4 and inhibition of endothelial cells of newborn rat eyes (75-77). BMP signaling regulates multiple key steps in embryonic development and differentiation and play crucial role in maintaining the homeostasis of vascular, reproductive, urogenital and nerves system. Dysregulatin in this pathway causes many diseases in adult such as malignancies (78).

In 2004 it was shown that *QSULF1* interferes in BMP signaling through releasing noggin from the cell surface to restore BMP response (79). While, in 2008 a more direct role of *XtSULF1* other than interacting with noggin was shown, it was claimed that over expression of xenpus *SULF1* blocks the p-smad/1 induction by BMP4 and reduces BMP4 interaction with the receptor, which can be due to changing HSPGs leading to less ligand-receptor interaction. Another means to effect the BMP signaling by over-expression of *XtSULF1* is ligand-receptor endocytosis into the cell (67). In 2010, Otsuki et al, showed that *SULF1* -/- up-regulates noggin expression in chondrocytes and also reduced *SULF1* decreases the BMP7 SMAD1/5 signaling (80). A study in 2012 on prostate development suggests that BMPs regulate *SULF1* expression (81). The latest confirmation on the impact of *SULF1* on BMP pathway was published on 2012, showing increased Gbb/BMP abundance and distribution in *SULF1* null Drosophila neuromuscular junction(65).

HGF and *SULF1*

Hepatocyte growth factor (HGF) belongs to the plasminogen subfamily of S1 peptidases

but has no detectable protease activity. It regulates cell growth, cell motility, and morphogenesis by activating a tyrosine kinase signaling cascade after binding to the proto-oncogenic c-Met receptor. Its ability to stimulate mitogenesis, cell motility, and matrix invasion gives it a central role in angiogenesis, tumorogenesis, and tissue regeneration. Other than mesenchymal secretion, HGF is shown to be expressed and secreted by endothelial cells and VSMC, which revealed characteristics of an endothelium-specific growth factor in both autocrine and paracrine manner (82). HGF promotes angiogenesis through positive regulation of VEGF and negative regulation of thrombospondin (83). It seems that HGF acts synergically with VEGF in angiogenesis, too (84). Many reports reveal the role of HGF in cancers and angiogenesis-related diseases (85-92). A report in 2004 for the first time showed that *SULF1* can modulate HGF cell signaling by desulfating cell surface HSGAG in hepatocellular cancer (18). This result was confirmed the same year on head and neck squamous cell carcinoma (SCCHN), which showed the role of *SULF1* on changing sulfate arrangement of HSGAGs, and thus its impact on Erk and Akt were observed (23). A study performed on 2012 on the impact of *SULF1* on sulfation of HS and HGF signaling in satellite-cell growth in an in vitro model of dissociated whole skeletal muscle fibers, gave another confirmation to the role of *SULF1*A in enhancing HGF signaling (93). HGF signaling is essential for organ development in fetal stage and also endogenous HGF is required for self-repair of many injuries such as liver and lung ones (94). HGF have a crucial role in many cancers such as colorectal cancer through MET signaling (95).

HB-EGF and *SULF1*

Heparin-binding EGF-like growth factor (HB-EGF) is a member of the epidermal growth factor (EGF)-like growth factor family of proteins that acts through binding to the EGF receptor (EGFR) and its associated receptors ERBB2, ERBB3 and ERBB4. The extended family comprises 15 members, all of which conform broadly to common structural framework centered on 6 cysteine residues in the sequence. Disulphide bond formation between 3 pairs of cysteines gives rise to the characteristic 3-looped EGF-like motif that mediates high-affinity binding to receptors. HB-EGF has a central role in angiogenesis, via enhancing migration of fibroblasts, endothelial cells and vascular smooth muscle cells. It has been shown that HB-EGF stimulates vascular formation in a VEGF comparable and independent manner through activation of PI3K, MAPK and eNOS (96-98). This is while VEGF up-regulates HB-EGf (99). Dysregulation in this pathway leads to many diseases including diabetic retinopathy, rheumatoid arthritis, psoriasis and many cancers such as gastric, ovarian and breast cancers (100-103).

Lia et al. in 2003 demonstrated that *SULF1* can inhibit the function of HB-EGF through EGF receptor by changing sulfate pattern of HS-GAG in ovarian cancer cell line, which was not observed for EGF, showing that it is not interacting with HS-GAG (15). Consistently, in 2007 a report showed the inhibitory function of *SULF1* on autocrine activated EGFR/Erk pathway in breast cancer cells, through the regulation of HB-EGF signaling (17).

SHH and *SULF1*

The sonic hedgehog (SHH) family signals through patched receptor, which releases SMO from a repressed state and allows it to signal by activating Gli transcription factor. This is called the canonical pathway of HH signaling. Although, it is identified that Hh acts in angiogenesis in a non-canonical pathway independent of SMO and Gli in endothelial cells, too (104,105). SHH signaling in angiogenesis is characterized by distinct large diameter vessels (106). Different studies have reported the impact of SHH signaling in angiogenesis by increasing circulating bone marrow-derived endothelial precursors and improving their contribution to

neovascularization (107). In addition, at least through inducing the expression of Ang1, Ang2, VEGF, FGF2, TGF, PDGF, CYR61, NOS and SDF-1α, it regulates growth, maturation and stabilization of vessels (106-121). SHH also interacts with FGF2 to balance maturation and branching of vessels through regulating Ang1 and Ang2 (116). It also acts in couple with HIF-α to regulate angiogenesis (120,122). SHH participates in both developmental and pathologic angiogenesis, as in a wide variety of cancers and angiogenesis-related diseases such as diabetic retinopathy and psoriasis. Also, it has been identified as a potential therapeutic agent for ischemic disease (105, 109, 110, 121, 123, 124).

Danesin et al. in 2006 by a study performed on chick embryo ventral neural progenitor, showed the contribution of *SULF1* with activation of SHH signaling by SHH/HSPG formation at the surface of receptor cell, thus concentrating and/or facilitating its presentation to receptor (125).

Conclusion

As it was shown in this review, *SULF1* has a crucial regulatory effect on VEGF, FGF, Wnt, BMP, HGF, HB-EGF, SHH, GDNF. It might also have regulatory effects on other growth factors such as PDGF. Almost all of these factors are involved in angiogenesis and regulate different aspects of both developmental and pathogenic angiogenesis. This candidates *SULF1* as a central player of angiogenic aspects of diseases and developmental defects, such as cancers, diabetic retinopathy, rheumatoid arthritis, psoriasis, recurrent pregnancy loss and other angiogenesis-related diseases. Therefore, studying mutations or possible polymorphisms of *SULF1* in these diseases could help us to detect those who are high-risk to develop the disease or are at risk for some complications such as diabetic retinopathy. Detecting these high-risk patients will improve their prognosis considerably.

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