

## Impact of *SULF1* Gene on Angiogenesis

Mohammad Hasan Sheikhha<sup>1</sup>, Eskandar Taghizadeh<sup>2</sup>, Mohammad Bagher Mahmoodi<sup>2</sup>, Seyed Mehdi Kalantar<sup>3\*</sup>

1- MD, PhD in Medical Molecular Genetics, Yazd Diabetes Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

2- MSc in Human Genetics, Genetics Department, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

3- PhD in Cytogenetic, Research and Clinical Center for Infertility, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

**\*Correspondence:**

Seyed Mehdi Kalantar, Research and Clinical Center for Infertility, Boali Avenue, Safayeh, Yazd, Iran.

**Fax:** (98) 351 824 7087

**Tel:** (98)351 824 7085

**Email:** smkalantar@yahoo.com

**Received:** 25 June 2013

**Accepted:** 10 August 2013

**Published in September 2013**

### 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/heparan 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 *-/-* hematopoietic 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/ $\beta$  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* (*xtSULF1*)(65-69); while in 2011, Jie Li et al reported that *SULF1* inhibits Wnt/ $\beta$  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 *CTNBN1*, which constitutively activates wnt/ $\beta$  catenin signaling pathway independent of Wnt (70). Sahota et al. showed that the novel shorter variant of *SULF1*, variant B, in contrast to *SULF1A* 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- $\beta$  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, ALK3/6 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. Dysregulation 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 xenopus *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 *SULF1A* 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-1 $\alpha$ , 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- $\alpha$  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.

## References

1. Sarrazin S, Lamanna WC, Esko JD. Heparan sulfate proteoglycans. Cold Spring Harbor Perspectives in Biology. 2011;3(7).
2. Tumova S, Woods A, Couchman JR. Heparan sulfate proteoglycans on the cell surface: versatile coordinators of cellular functions. The international journal of biochemistry & cell biology. 2000;32(3):269-88.
3. Backen AC, Cole CL, Lau SC, Clamp AR, McVey R, Gallagher JT, et al. Heparan sulphate synthetic and editing enzymes in ovarian cancer. British journal of cancer. 2007;96(10):1544-8.
4. Bernfield M, Götte M, Park PW, Reizes O, Fitzgerald ML, Lincecum J, et al. Functions of cell surface heparan sulfate proteoglycans. Annual review of biochemistry. 1999;68(1):729-77.
5. Lamanna WC, Baldwin RJ, Padva M, Kalus I, Ten Dam G, Van Kuppevelt TH, et al. Heparan sulfate 6-O-endosulfatases: discrete in vivo activities and functional co-operativity. Biochemical journal. 2006;400(1):63.
6. Lin X. Functions of heparan sulfate proteoglycans in cell signaling during development. Development. 2004;131(24):6009-21.
7. Dhoot GK, Gustafsson MK, Ai X, Sun W, Standiford DM, Emerson Jr CP. Regulation of Wnt signaling and embryo patterning by an extracellular sulfatase. Science Signalling. 2001;293(5535):1663.
8. Morimoto-Tomita M, Uchimura K, Werb Z, Hemmerich S, Rosen SD. Cloning and characterization of two extracellular heparin-degrading endosulfatases in mice and humans. Journal of Biological Chemistry. 2002;277(51):49175-85.
9. Parenti G, Meroni G, Ballabio A. The sulfatase gene family. Current opinion in genetics & development. 1997;7(3):386-91.
10. Ghosh D. Three-Dimensional Structures of Sulfatases. Methods in enzymology. 2005;400:273-93.
11. Waldow A, Schmidt B, Dierks T, von Bülow R, von Figura K. Amino acid residues forming the active site of arylsulfatase A. Journal of Biological Chemistry. 1999;274(18):12284-8.
12. Ambasta RK, Ai X, Emerson Jr CP. Quail Sulfl function requires asparagine-linked glycosylation.

- Journal of Biological Chemistry. 2007;282(47):34492-9.
13. Frese MA, Milz F, Dick M, Lamanna WC, Dierks T. Characterization of the human sulfatase sulf1 and its high affinity heparin/heparan sulfate interaction domain. *Journal of Biological Chemistry*. 2009;284(41):28033-44.
  14. Lamanna WC, Frese MA, Balleininger M, Dierks T. Sulf loss influences N-, 2-O-, and 6-O-sulfation of multiple heparan sulfate proteoglycans and modulates fibroblast growth factor signaling. *Journal of Biological Chemistry*. 2008;283(41):27724-35.
  15. Lai J, Chien J, Staub J, Avula R, Greene EL, Matthews TA, et al. Loss of HSulf-1 up-regulates heparin-binding growth factor signaling in cancer. *Journal of Biological Chemistry*. 2003;278(25):23107-17.
  16. Narita K, Staub J, Chien J, Meyer K, Bauer M, Friedl A, et al. HSulf-1 inhibits angiogenesis and tumorigenesis in vivo. *Cancer research*. 2006;66(12):6025-32.
  17. Narita K, Chien J, Mullany SA, Staub J, Qian X, Lingle WL, et al. Loss of HSulf-1 expression enhances autocrine signaling mediated by amphiregulin in breast cancer. *Journal of Biological Chemistry*. 2007;282(19):14413-20.
  18. Lai J, Chien JR, Moser DR, Staub JK, Aderca I, Montoya DP, et al. hSulf1 Sulfatase promotes apoptosis of hepatocellular cancer cells by decreasing heparin-binding growth factor signaling. *Gastroenterology*. 2004;126(1):231-48.
  19. Lai JP, Yu C, Moser CD, Aderca I, Han T, Garvey TD, et al. SULF1 inhibits tumor growth and potentiates the effects of histone deacetylase inhibitors in hepatocellular carcinoma. *Gastroenterology*. 2006;130(7):2130-44.
  20. Li J, Kleeff J, Abiatari I, Kayed H, Giese NA, Felix K, et al. Enhanced levels of Hsulf-1 interfere with heparin-binding growth factor signaling in pancreatic cancer. *Molecular cancer*. 2005;4(1):14.
  21. Abiatari I, Kleeff J, Li J, Felix K, Büchler MW, Friess H. Hsulf-1 regulates growth and invasion of pancreatic cancer cells. *Journal of clinical pathology*. 2006;59(10):1052-8.
  22. Dai Y, Yang Y, MacLeod V, Yue X, Rapraeger AC, Shriver Z, et al. HSulf-1 and HSulf-2 are potent inhibitors of myeloma tumor growth in vivo. *Journal of Biological Chemistry*. 2005;280(48):40066-73.
  23. Lai JP, Chien J, Strome SE, Staub J, Montoya DP, Greene EL, et al. HSulf-1 modulates HGF-mediated tumor cell invasion and signaling in head and neck squamous carcinoma. *Oncogene*. 2004;23(7):1439-47.
  24. Clauss M, editor. *Molecular biology of the VEGF and the VEGF receptor family*. Seminars in thrombosis and hemostasis; 2000.
  25. Cohen T, Gitay-Goren H, Sharon R, Shibuya M, Halaban R, Levi B, et al. VEGF121, a vascular endothelial growth factor (VEGF) isoform lacking heparin binding ability, requires cell-surface heparan sulfates for efficient binding to the VEGF receptors of human melanoma cells. *Journal of Biological Chemistry*. 1995;270(19):11322-6.
  26. Gerber HP, McMurtrey A, Kowalski J, Yan M, Keyt BA, Dixit V, et al. Vascular endothelial growth factor regulates endothelial cell survival through the phosphatidylinositol 3'-kinase/Akt signal transduction pathway. *Journal of Biological Chemistry*. 1998;273(46):30336-43.
  27. Albig AR, Schiemann WP. Fibulin-5 antagonizes vascular endothelial growth factor (VEGF) signaling and angiogenic sprouting by endothelial cells. *DNA and cell biology*. 2004;23(6):367-79.
  28. Seko Y, Takahashi N, Tobe K, Ueki K, Kadowaki T, Yazaki Y. Vascular endothelial growth factor (VEGF) activates Raf-1, mitogen-activated protein (MAP) kinases, and S6 kinase (p90rsk) in cultured rat cardiac myocytes. *Journal of cellular physiology*. 1998;175(3):239-46.
  29. Narita K, Staub J, Chien J, Meyer K, Bauer M, Friedl A, et al. HSulf-1 inhibits angiogenesis and tumorigenesis in vivo. *Cancer research*. 2006;66(12):6025-32. Epub 2006/06/17.
  30. Uchimura K, Morimoto-Tomita M, Rosen SD. Measuring the activities of the Sulfs: two novel heparin/heparan sulfate endosulfatases. *Methods in enzymology*. 2006;416:243-53.
  31. Harmey JH. *VEGF and Cancer*: Springer; 2004.
  32. Canavese M, Altruda F, Ruzicka T, Schaubert J. Vascular endothelial growth factor (VEGF) in the pathogenesis of psoriasis—A possible target for novel therapies? *Journal of dermatological science*. 2010;58(3):171-6.
  33. Paleolog EM, Young S, Stark AC, McCloskey RV, Feldmann M, Maini RN. Modulation of angiogenic vascular endothelial growth factor by tumor necrosis factor  $\alpha$  and interleukin-1 in rheumatoid arthritis. *Arthritis & Rheumatism*. 2004;41(7):1258-65.
  34. Awata T, Inoue K, Kurihara S, Ohkubo T, Watanabe M, Inukai K, et al. A common polymorphism in the 5'-untranslated region of the VEGF gene is associated with diabetic retinopathy in type 2 diabetes. *Diabetes*. 2002;51(5):1635-9.
  35. Beenken A, Mohammadi M. The FGF family: biology, pathophysiology and therapy. *Nature Reviews Drug Discovery*. 2009;8(3):235-53.
  36. Kovacs D, Falchi M, Cardinali G, Raffa S, Carducci M, Cota C, et al. Immunohistochemical analysis of keratinocyte growth factor and fibroblast growth factor 10 expression in psoriasis. *Experimental dermatology*. 2005;14(2):130-7.
  37. Malemud CJ. Growth hormone, VEGF and FGF: involvement in rheumatoid arthritis. *Clinica*

- chimica acta; international journal of clinical chemistry. 2007;375(1-2):10.
38. Penault-Llorca F, Bertucci F, Adélaïde J, Parc P, Coulier F, Jacquemier J, et al. Expression of FGF and FGF receptor genes in human breast cancer. *International journal of cancer*. 2006;61(2):170-6.
  39. Hanneken A, de Juan Jr E, Luty GA, Fox GM, Schiffer S, Hjelmeland LM. Altered distribution of basic fibroblast growth factor in diabetic retinopathy. *Archives of ophthalmology*. 1991;109(7):1005.
  40. Lai JP, Chien JR, Moser DR, Staub JK, Aderca I, Montoya DP, et al. hSulf1 Sulfatase promotes apoptosis of hepatocellular cancer cells by decreasing heparin-binding growth factor signaling. *Gastroenterology*. 2004;126(1):231-48. Epub 2003/12/31.
  41. Li J, Kleff J, Abiatari I, Kayed H, Giese NA, Felix K, et al. Enhanced levels of Hsulf-1 interfere with heparin-binding growth factor signaling in pancreatic cancer. *Molecular cancer*. 2005;4(1):14. Epub 2005/04/09.
  42. Zhao W, Allen S, Dhoot GK. FGF mediated Sulf1 regulation. *FEBS letters*. 2007;581(25):4960-4. Epub 2007/10/02.
  43. Freeman SD, Moore WM, Guiral EC, Holme AD, Turnbull JE, Pownall ME. Extracellular regulation of developmental cell signaling by XtSulf1. *Developmental biology*. 2008;320(2):436-45. Epub 2008/07/12.
  44. Winterbottom EF, Pownall ME. Complementary expression of HSPG 6-O-endosulfatases and 6-O-sulfotransferase in the hindbrain of *Xenopus laevis*. *Gene expression patterns : GEP*. 2009;9(3):166-72. Epub 2008/12/09.
  45. Otsuki S, Hanson SR, Miyaki S, Grogan SP, Kinoshita M, Asahara H, et al. Extracellular sulfatases support cartilage homeostasis by regulating BMP and FGF signaling pathways. *Proceedings of the National Academy of Sciences of the United States of America*. 2010;107(22):10202-7. Epub 2010/05/19.
  46. Buono M, Visigalli I, Bergamasco R, Biffi A, Cosma MP. Sulfatase modifying factor 1-mediated fibroblast growth factor signaling primes hematopoietic multilineage development. *The Journal of experimental medicine*. 2010;207(8):1647-60. Epub 2010/07/21.
  47. van Amerongen R, Mikels A, Nusse R. Alternative wnt signaling is initiated by distinct receptors. *Science Signalling*. 2008;1(35):re9.
  48. Seifert JRK, Mlodzik M. Frizzled/PCP signalling: a conserved mechanism regulating cell polarity and directed motility. *Nature Reviews Genetics*. 2007;8(2):126-38.
  49. Goodwin AM, Sullivan KM, D'Amore PA. Cultured endothelial cells display endogenous activation of the canonical Wnt signaling pathway and express multiple ligands, receptors, and secreted modulators of Wnt signaling. *Developmental dynamics*. 2006;235(11):3110-20.
  50. Favre CJ, Mancuso M, Maas K, McLean JW, Baluk P, McDonald DM. Expression of genes involved in vascular development and angiogenesis in endothelial cells of adult lung. *American Journal of Physiology-Heart and Circulatory Physiology*. 2003;285(5):H1917-H38.
  51. van Gijn ME, Blankesteyn WM, Smits JFM, Hierck B, Gittenberger-de Groot AC. Frizzled 2 is transiently expressed in neural crest-containing areas during development of the heart and great arteries in the mouse. *Anatomy and embryology*. 2001;203(3):185-92.
  52. Mao C, Malek OTB, Pueyo ME, Steg PG, Soubrier F. Differential expression of rat frizzled-related frzb-1 and frizzled receptor fz1 and fz2 genes in the rat aorta after balloon injury. *Arteriosclerosis, thrombosis, and vascular biology*. 2000;20(1):43-51.
  53. Wright M, Aikawa M, Szeto W, Papkoff J. Identification of a Wnt-responsive signal transduction pathway in primary endothelial cells. *Biochemical and biophysical research communications*. 1999;263(2):384-8.
  54. Chamorro MN, Schwartz DR, Vonica A, Brivanlou AH, Cho KR, Varmus HE. FGF-20 and DKK1 are transcriptional targets of  $\beta$ -catenin and FGF-20 is implicated in cancer and development. *The EMBO journal*. 2004;24(1):73-84.
  55. Kaykas A, Yang-Snyder J, Héroux M, Shah KV, Bouvier M, Moon RT. Mutant Frizzled 4 associated with vitreoretinopathy traps wild-type Frizzled in the endoplasmic reticulum by oligomerization. *Nature cell biology*. 2003;6(1):52-8.
  56. Kühl M, Sheldahl LC, Park M, Miller JR, Moon RT. The Wnt/Ca<sup>2+</sup> pathway: a new vertebrate Wnt signaling pathway takes shape. *Trends in genetics*. 2000;16(7):279-83.
  57. Mann B, Gelos M, Siedow A, Hanski M, Gratchev A, Ilyas M, et al. Target genes of  $\beta$ -catenin-T cell-factor/lymphoid-enhancer-factor signaling in human colorectal carcinomas. *Proceedings of the National Academy of Sciences*. 1999;96(4):1603-8.
  58. Kawabata K, Murakami A, Ohigashi H. Nobiletin, a citrus flavonoid, down-regulates matrix metalloproteinase-7 (matrilysin) expression in HT-29 human colorectal cancer cells. *Bioscience, biotechnology, and biochemistry*. 2005;69(2):307-14.
  59. Cheng C, Yeh J, Fan TP, Smith SK, Charnock-Jones DS. Wnt5a-mediated non-canonical Wnt signalling regulates human endothelial cell proliferation and migration. *Biochemical and biophysical research communications*. 2008;365(2):285-90.

60. Newman AC, Hughes CCW. Macrophages and angiogenesis: A role for Wnt signaling. *Vascular*. 2012;4:13.
61. Zerlin M, Julius MA, Kitajewski J. Wnt/Frizzled signaling in angiogenesis. *Angiogenesis*. 2008;11(1):63-9.
62. Clevers H, Nusse R. Wnt/beta-catenin signaling and disease. *Cell*. 2012;149(6):1192-205.
63. Gudjonsson JE, Johnston A, Stoll SW, Riblett MB, Xing X, Kochkodan JJ, et al. Evidence for altered Wnt signaling in psoriatic skin. *The Journal of investigative dermatology*. 2010;130(7):1849-59.
64. Chen Y, Hu Y, Zhou T, Zhou KK, Mott R, Wu M, et al. Activation of the Wnt pathway plays a pathogenic role in diabetic retinopathy in humans and animal models. *The American journal of pathology*. 2009;175(6):2676-85.
65. Dani N, Nahm M, Lee S, Brodie K. A Targeted Glycan-Related Gene Screen Reveals Heparan Sulfate Proteoglycan Sulfation Regulates Wnt and BMP Trans-Synaptic Signaling. *PLoS Genetics*. 2012;8(11):e1003031.
66. Yang JD, Sun Z, Hu C, Lai J, Dove R, Nakamura I, et al. Sulfatase 1 and sulfatase 2 in hepatocellular carcinoma: associated signaling pathways, tumor phenotypes, and survival. *Genes, Chromosomes and Cancer*. 2011;50(2):122-35.
67. Freeman SD, Moore WM, Guiral EC, Holme AD, Turnbull JE, Pownall ME. Extracellular regulation of developmental cell signaling by XtSulf1. *Developmental biology*. 2008;320(2):436-45.
68. Nawroth R, Van Zante A, Cervantes S, McManus M, Hebrok M, Rosen SD. Extracellular sulfatases, elements of the Wnt signaling pathway, positively regulate growth and tumorigenicity of human pancreatic cancer cells. *PLoS One*. 2007;2(4):e392.
69. Hayano S, Kurosaka H, Yanagita T, Kalus I, Milz F, Ishihara Y, et al. Roles of heparan sulfate sulfation in dentinogenesis. *Journal of Biological Chemistry*. 2012;287(15):12217-29.
70. Li J, Mo ML, Chen Z, Yang J, Li QS, Wang DJ, et al. HSulf-1 inhibits cell proliferation and invasion in human gastric cancer. *Cancer science*. 2011;102(10):1815-21.
71. Sahota AP, Dhoot GK. A novel SULF1 splice variant inhibits Wnt signalling but enhances angiogenesis by opposing SULF1 activity. *Experimental cell research*. 2009;315(16):2752-64.
72. Deckers MML, van Bezooijen RL, van der Horst G, Hoogendam J, van der Bent C, Papapoulos SE, et al. Bone morphogenetic proteins stimulate angiogenesis through osteoblast-derived vascular endothelial growth factor A. *Endocrinology*. 2002;143(4):1545-53.
73. David L, Feige JJ, Bailly S. Emerging role of bone morphogenetic proteins in angiogenesis. *Cytokine & growth factor reviews*. 2009;20(3):203-12.
74. Sasai Y, De Robertis EM. Ectodermal patterning in vertebrate embryos. *Developmental biology*. 1997;182(1):5.
75. Kiyono M, Shibuya M. Bone morphogenetic protein 4 mediates apoptosis of capillary endothelial cells during rat pupillary membrane regression. *Molecular and cellular biology*. 2003;23(13):4627-36.
76. Nimmagadda S, Geetha Loganathan P, Huang R, Scaal M, Schmidt C, Christ B. BMP4 and noggin control embryonic blood vessel formation by antagonistic regulation of VEGFR-2 (Quek1) expression. *Developmental biology*. 2005;280(1):100-10.
77. Reese DE, Hall CE, Mikawa T. Negative regulation of midline vascular development by the notochord. *Developmental cell*. 2004;6(5):699-708.
78. Jeong J, Kang DI, Lee GT, Kim IY. Bone Morphogenetic Protein Signaling: Implications in Urology. *Korean J Urol*. 2010;51(8):511-7.
79. Viviano BL, Paine-Saunders S, Gasiunas N, Gallagher J, Saunders S. Domain-specific modification of heparan sulfate by Qsulf1 modulates the binding of the bone morphogenetic protein antagonist Noggin. *Journal of Biological Chemistry*. 2004;279(7):5604-11.
80. Otsuki S, Hanson SR, Miyaki S, Grogan SP, Kinoshita M, Asahara H, et al. Extracellular sulfatases support cartilage homeostasis by regulating BMP and FGF signaling pathways. *Proceedings of the National Academy of Sciences*. 2010;107(22):10202-7.
81. Buresh-Stiemke RA, Malinowski RL, Keil KP, Vezina CM, Oosterhof A, Van Kuppevelt TH, et al. Distinct expression patterns of Sulf1 and Hs6st1 spatially regulate heparan sulfate sulfation during prostate development. *Developmental dynamics*. 2012.
82. Nakamura Y, Morishita R, Higaki J, Kida I, Aoki M, Moriguchi A, et al. Expression of local hepatocyte growth factor system in vascular tissues. *Biochemical and biophysical research communications*. 1995;215(2):483-8.
83. Neill T, Painter H, Buraschi S, Owens RT, Lisanti MP, Schaefer L, et al. Decorin Antagonizes the Angiogenic Network concurrent inhibition of MET, hypoxia inducible factor 1 $\alpha$ , vascular endothelial growth factor a, and induction of thrombospondin-1 and TIMP3. *Journal of Biological Chemistry*. 2012;287(8):5492-506.
84. Xin X, Yang S, Ingle G, Zlot C, Rangell L, Kowalski J, et al. Hepatocyte Growth Factor Enhances Vascular Endothelial Growth Factor-Induced Angiogenesis in Vitro and in Vivo. *The American journal of pathology*. 2001;158(3):1111-20.
85. Di Renzo MF, Olivero M, Katsaros D, Crepaldi T, Gaglia P, Zola P, et al. Overexpression of the

- Met/HGF receptor in ovarian cancer. International journal of cancer. 2006;58(5):658-62.
86. Ide T, Kitajima Y, Miyoshi A, Ohtsuka T, Mitsuno M, Ohtaka K, et al. The hypoxic environment in tumor-stromal cells accelerates pancreatic cancer progression via the activation of paracrine hepatocyte growth factor/c-Met signaling. *Annals of surgical oncology*. 2007;14(9):2600-7.
  87. Parr C, Hiscox S, Nakamura T, Matsumoto K, Jiang WG. Nk4, a new HGF/SF variant, is an antagonist to the influence of HGF/SF on the motility and invasion of colon cancer cells. *International journal of cancer*. 2000;85(4):563-70.
  88. Nakamura T, Mizuno S, Matsumoto K, Sawa Y, Matsuda H. Myocardial protection from ischemia/reperfusion injury by endogenous and exogenous HGF. *Journal of Clinical Investigation*. 2000;106(12):1511-9.
  89. Woodbury RL, Varnum SM, Zangar RC. Elevated HGF levels in sera from breast cancer patients detected using a protein microarray ELISA. *Journal of proteome research*. 2002;1(3):233-7.
  90. Parr C, Jiang WG. Expression of hepatocyte growth factor/scatter factor, its activator, inhibitors and the c-Met receptor in human cancer cells. *International journal of oncology*. 2001;19(4):857.
  91. Lashkari K, Hirose T, Yazdany J, McMeel JW, Kazlauskas A, Rahimi N. Vascular endothelial growth factor and hepatocyte growth factor levels are differentially elevated in patients with advanced retinopathy of prematurity. *The American journal of pathology*. 2000;156(4):1337-44.
  92. Feuerherm A, Børset M, Seidel C, Sundan A, Leisstad L. Elevated levels of osteoprotegerin (OPG) and hepatocyte growth factor (HGF) in rheumatoid arthritis. *Scandinavian journal of rheumatology*. 2001;30(4):229-34.
  93. Gill R, Hitchins L, Fletcher F, Dhoot GK. SulflA and HGF regulate satellite-cell growth. *Journal of Cell Science*. 2010;123(11):1873-83.
  94. Nakamura T, Mizuno S. The discovery of Hepatocyte Growth Factor (HGF) and its significance for cell biology, life sciences and clinical medicine. *Proc Jpn Acad Ser B Phys Biol Sci*. 2010;86(6):588-610.
  95. Liska D, Chen CT, Bachleitner-Hofmann T, Christensen JG, Weiser MR, Hwang CI, et al. HGF rescues colorectal cancer cells from EGFR inhibition via MET activation  
MET-dependent cancer invasion may be preprogrammed by early alterations of p53-regulated feedforward loop and triggered by stromal cell-derived HGF. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2011;17(3):472-82.
  96. El-Assal ON, Paddock H, Marquez A, Besner GE. HB-EGF gene disruption is associated with delayed intestinal restitution, impaired angiogenesis and poor survival after intestinal ischemia in mice. *Journal of pediatric surgery*. 2008;43(6):1182.
  97. Mehta VB, Besner GE. HB-EGF promotes angiogenesis in endothelial cells via PI3-kinase and MAPK signaling pathways. *Growth Factors*. 2007;25(4):253-63.
  98. Wilson KJ, Gilmore JL, Foley J, Lemmon MA, Riese II DJ. Functional selectivity of EGF family peptide growth factors: implications for cancer. *Pharmacology & therapeutics*. 2009;122(1):1-8.
  99. Arkonac BM, Foster LC, Sibinga NES, Patterson C, Lai K, Tsai JC, et al. Vascular endothelial growth factor induces heparin-binding epidermal growth factor-like growth factor in vascular endothelial cells. *Journal of Biological Chemistry*. 1998;273(8):4400-5.
  100. Matsumoto S, Kishida K, Shimomura I, Maeda N, Nagaretani H, Matsuda M, et al. Increased plasma HB-EGF associated with obesity and coronary artery disease. *Biochemical and biophysical research communications*. 2002;292(3):781-6.
  101. Cook PW, Piepkorn M, Clegg CH, Plowman GD, DeMay JM, Brown JR, et al. Transgenic expression of the human amphiregulin gene induces a psoriasis-like phenotype. *Journal of Clinical Investigation*. 1997;100(9):2286.
  102. Schulz B, Pruessmeyer J, Maretzky T, Ludwig A, Blobel CP, Saftig P, et al. ADAM10 regulates endothelial permeability and T-Cell transmigration by proteolysis of vascular endothelial cadherin. *Circulation research*. 2008;102(10):1192-201.
  103. Yamane S, Ishida S, Hanamoto Y, Kumagai K, Masuda R, Tanaka K, et al. Proinflammatory role of amphiregulin, an epidermal growth factor family member whose expression is augmented in rheumatoid arthritis patients. *J Inflamm (Lond)*. 2008;5:5.
  104. Chinchilla P, Xiao L, Kazanietz MG, Riobo NA. Hedgehog proteins activate pro-angiogenic responses in endothelial cells through non-canonical signaling pathways. *Cell Cycle*. 2010;9(3):570-9.
  105. Honami T, Shimo T, Okui T, Kurio N, Hassan NMM, Iwamoto M, et al. Sonic hedgehog signaling promotes growth of oral squamous cell carcinoma cells associated with bone destruction. *Oral oncology*. 2012;48(1):49-55.
  106. Pola R, Ling LE, Silver M, Corbley MJ, Kearney M, Pepinsky RB, et al. The morphogen Sonic hedgehog is an indirect angiogenic agent upregulating two families of angiogenic growth factors. *Nature medicine*. 2001;7(6):706-11.
  107. Palladino M, Gatto I, Neri V, Straino S, Silver M, Tritarelli A, et al. Pleiotropic beneficial effects of sonic hedgehog gene therapy in an experimental model of peripheral limb ischemia. *Molecular Therapy*. 2011;19(4):658-66.

108. Olsen CL, Hsu PP, Glienke J, Rubanyi GM, Brooks AR. Hedgehog-interacting protein is highly expressed in endothelial cells but down-regulated during angiogenesis and in several human tumors. *BMC cancer*. 2004;4(1):43.
109. Surace EM, Balaggan KS, Tessitore A, Mussolino C, Cotugno G, Bonetti C, et al. Inhibition of ocular neovascularization by hedgehog blockade. *Molecular Therapy*. 2006;13(3):573-9.
110. Nagase T, Nagase M, Yoshimura K, Fujita T, Koshima I. Angiogenesis within the developing mouse neural tube is dependent on sonic hedgehog signaling: possible roles of motor neurons. *Genes to Cells*. 2005;10(6):595-604.
111. Nagase T, Nagase M, Yoshimura K, Machida M, Yamagishi M. Defects in aortic fusion and craniofacial vasculature in the holoprosencephalic mouse embryo under inhibition of sonic hedgehog signaling. *Journal of Craniofacial Surgery*. 2006;17(4):736.
112. Lee SW, Moskowitz MA, Sims JR. Sonic hedgehog inversely regulates the expression of angiopoietin-1 and angiopoietin-2 in fibroblasts. *International journal of molecular medicine*. 2007;19(3):445.
113. Straface G, Aprahamian T, Flex A, Gaetani E, Biscetti F, Smith RC, et al. Sonic hedgehog regulates angiogenesis and myogenesis during post-natal skeletal muscle regeneration. *Journal of cellular and molecular medicine*. 2009;13(8):2424-35.
114. Dohle E, Fuchs S, Kolbe M, Hofmann A, Schmidt H, Kirkpatrick CJ. Sonic hedgehog promotes angiogenesis and osteogenesis in a coculture system consisting of primary osteoblasts and outgrowth endothelial cells. *Tissue Engineering Part A*. 2010;16(4):1235-7.
115. Ahmed RPH, Haider KH, Shujia J, Afzal MR, Ashraf M. Sonic Hedgehog gene delivery to the rodent heart promotes angiogenesis via iNOS/netrin-1/PKC pathway. *PLoS One*. 2010;5(1):e8576.
116. Fujii T, Kuwano H. Regulation of the expression balance of angiopoietin-1 and angiopoietin-2 by Shh and FGF-2. *In Vitro Cellular & Developmental Biology-Animal*. 2010;46(6):487-91.
117. Benameur T, Soleti R, Porro C, Andriantsitohaina R, Martínez MC. Microparticles carrying Sonic hedgehog favor neovascularization through the activation of nitric oxide pathway in mice. *PLoS One*. 2010;5(9):e12688.
118. Dohle E, Fuchs S, Kolbe M, Hofmann A, Schmidt H, Kirkpatrick CJ. Comparative study assessing effects of sonic hedgehog and VEGF in a human co-culture model for bone vascularisation strategies. *European Cells and Materials*. 2011;21:144-56.
119. Fuchs S, Dohle E, Kirkpatrick C. Sonic Hedgehog-mediated synergistic effects guiding angiogenesis and osteogenesis. *Vitamins and hormones*. 2012;88:491-506.
120. Sekiguchi H, Ii M, Jujo K, Renault MA, Thorne T, Clarke T, et al. Estradiol triggers sonic-hedgehog-induced angiogenesis during peripheral nerve regeneration by downregulating hedgehog-interacting protein. *Laboratory Investigation*. 2012;92(4):532-42.
121. Cai J, Huang Y, Chen X, Xie H, Deng L. Regulation of sonic hedgehog on vascular endothelial growth factor, basic fibroblast growth factor expression and secretion in bone marrow mesenchymal stem cells. *Zhongguo xiu fu chong jian wai ke za zhi= Zhongguo xiu fu chongjian waike zazhi= Chinese journal of reparative and reconstructive surgery*. 2012;26(1):112.
122. Hwang JM, Weng YJ, Lin JA, Bau DT, Ko FY, Tsai FJ, et al. Hypoxia-induced compensatory effect as related to Shh and HIF-1 $\alpha$  in ischemia embryo rat heart. *Molecular and cellular biochemistry*. 2008;311(1):179-87.
123. Teng H, Chopp M, Hozeska-Solgot A, Shen L, Lu M, Tang C, et al. Tissue Plasminogen Activator and Plasminogen Activator Inhibitor 1 Contribute to Sonic Hedgehog-Induced In Vitro Cerebral Angiogenesis. *PLoS One*. 2012;7(3):e33444.
124. Soleti R, Martínez MC. SoNlc Hedgehog on Microparticles and Neovascularization. *Hedgehog Signaling*. 2012:395.
125. Danesin C, Agius E, Escalas N, Ai X, Emerson C, Cochard P, et al. Ventral neural progenitors switch toward an oligodendroglial fate in response to increased Sonic hedgehog (Shh) activity: involvement of Sulfatase 1 in modulating Shh signaling in the ventral spinal cord. *The Journal of neuroscience*. 2006;26(19):5037-48.