Hemangioma Endothelial Cells and Hemangioma Stem Cells in Infantile Hemangioma

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Background: Hemangioma is one of the most common benign tumors in infants and young children. The 2 most important cells in the course of infantile hemangioma (IH) are hemangioma stem cells (HemSCs) and hemangioma endothelial cells (HemECs). Infantile hemangioma is characterized by massive proliferation of HemECs, but current studies indicate that HemSCs play an important role in pathogenesis of IH.

Objective: This review aimed to identify molecules that influence HemSC differentiation and HemEC proliferation and apoptosis to help clarify the pathogenesis of IH and provide novel drug targets for the treatment of IH.

Methods: Relevant basic science studies related to IH were identified by searching Google Scholar, Embase, PubMed, MEDLINE, and peer-reviewed journal articles.

Result: Hemangioma stem cells can differentiate into HemECs, pericytes, and adipocytes. In the proliferating phase of IH, HemSCs mainly differentiate into HemECs and pericytes to promote angiogenesis. In the regressive phase, they mainly differentiate into adipocytes. Therefore, increasing the proportion of HemSCs differentiating into adipocytes, inhibiting the proliferation of HemECs, and promoting the apoptosis of HemECs can facilitate the regression of IH.

Key Words: infantile hemangioma, hemangioma stem cells, hemangioma endothelial cells, differentiation, apoptosis

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The most common benign vascular tumor of infancy is hemangioma, and approximately 3% to 12% of new born children experienced this disease.[1–3] Infantile hemangioma (IH) usually occurs within a few days after birth and is divided into 3 phases: proliferating phase, involuting phase, and involuted phase.[4] The proliferating phase is characterized by proliferation of a large number of endothelial cells (ECs). During involuting phase, lesions gradually become adipose and fibrous tissues. During the involuted phase, EC proliferation and fibrofatty infiltration coexist in IH lesions.[5] Most of IHs has very small lesions and is not life-threatening, but it may affect the child's health and disfigurement.[6] Although most lesions will spontaneously regress, a small part requires clinical intervention. Currently, treatments for IH consist of β-blockers, corticosteroids, interferon α, vincristine, imiquimod, bleomycin A5, ACE inhibitor laser therapy, and surgical excision.[7] However, these treatments are partly effective, with adverse reactions, or cannot prevent the recurrence of hemangioma. Therefore, studies on the pathogenesis of IHs could provide new therapeutic strategies for IH.

Infantile hemangioma is a benign tumor characterized by massive increased ECs.[8] The proliferation of HemECs leads to disorder of angiogenesis, thus forming hemangioma. However, in animal model, it has been shown that HemECs did not initiate the occurrence in mice. Glucose transporter 1 (GLUT1) is a kind of glycolytic gene, which is specifically express in T-lymphocytes, erythrocytes, and ECs from brain and placenta. It is a marker of IH that can distinguish hemangioma from other vascular malformation.[9,10] GLUT1$^+$ cells isolated from IH have stem cell characteristics that can differentiate into endothelial, pericytic and adipogenic. GLUT1$^+$ HemECs decrease in the involuting phase of IH, implying that a number of stem cells are reduced with the regress of IH.[10] GLUT1$^+$ cells are similar to hemangioma stem cells (HemSCs) but not the same. Hemangioma stem cells are isolated from IH and specifically express SALL4 and CD133.

In this review, we aim to elucidate the current molecules that influence the differentiation of HemSCs and the development of HemECs to explore the pathogenesis of IH and more effective treatment of IH.

Hemangioma ECs in IH

Endothelial cell is the most significant component of blood vessel, which has histological characteristics of pebble shape. The vessel structure is supported by ECs and pericytes. During angiogenesis, ECs are activated, then proliferate and migrate along with the vascular endothelial growth factor (VEGF) gradient, aggregate, and form new blood vessels.[11,12] Vascular endothelial growth factor family includes VEGF A, B, C, D, and PIGF (placental growth factor) in mammals with 3 specific receptors (VEGF receptor 1 [VEGFR1], VEGFR2, VEGFR3) and 2 coreceptors (neuropilin 1 or 2).[13–15] They play a crucial role in angiogenesis. Infantile hemangioma lesions are composed of a large number of disordered blood vessels.[16] Hemangioma ECs (HemECs) proliferate inordinately, migrate, and aggregate to form disorganized vessels, which is manifested as IH. Changes in the number of HemECs affect the progression of IH. There are many factors affecting the proliferation, migration, and apoptosis of HemECs. Some studies have shown that VEGF,[14,17] microRNA (miRNA),[18,19] long noncoding RNAs (lncRNAs),[3] and other various molecules are abnormally expressed in IH. MicroRNA is a member of a small RNA family of approximately 20 nucleotides that functions by modulating mRNA.[20] Long noncoding RNAs are long noncoding transcripts of more than 200 nucleotides, and a total of 1259 and 857 lncRNAs are upregulated and downregulated, respectively, in IH by microarray analysis.[3,21] Elucidating molecular mechanisms of action on HemEC proliferation, migration, and apoptosis have shown the benefits to the treatment of IH (Fig. 1). For example, the mechanism of ACE inhibitor treatment for IH is via regulating the proliferation of HemECs.[7] Propranolol can inhibit the invasion and proliferation of HemECs to resist IH.[22] The key molecules that affect HemECs were listed in Table 1.

Proliferation and Migration of HemECs in IH

The proliferation and migration of HemECs are affected by multiple signals. AKT is a serine/threonine kinase, which plays a crucial role in HemEC proliferation, division, and migration.[18] COSMC (C1GALT1-specific chaperone 1) is a molecular chaperone of active T synthase, its expression is dependent on COSMC, and they are necessary for angiogenesis.[23] COSMC is highly expressed during the proliferative phase of IH, which promotes the proliferation of HemECs by enhancing the phosphorylation of VEGF receptor 2 and downstream AKT and ERK.[24]

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TABLE 1. Molecules Affecting HemECs

Influence Direction	Related Molecules	Target Signal
Promote proliferation	COSMC, PP2A	AKT, ERK
	PRR	Wnt
	NDRG1	RICTOR
	IL-6, lncRNA SNHG16	STAT3
	ID-1	PI3K/AKT/mTOR
	miR-130a	FAK/PI3K/Rac1/mdm2
	miR-15a/miR-205/ miR-501	AKT3/AKT1/HOXD10
	FABP4	mTOR
	lncRNA CASC9/ OIP5-AS1	miR-125a-3p-Nrg1 axis/NOB1
Inhibit proliferation	PEDF, FOXO1, miRNA-206	Unclear
	miR-424	ERK1/2
	lncRNA MEG3	PI3K/AKT
	lncRNA UCA1	mTOR/AMPK/Wnt/β
Affect apoptosis	PCNA	AKT/mTOR
	IGF-II	PI3K/AKT
	ID-1	PI3K/AKT/mTOR
	VEGF/VEGFR-2	PI3K/AKT
	lncRNA NEAT1	miR-361-5p-VEGFA
	linc00152	AKT/mTOR and Notch1

IL-6 indicates interleukin 6.

Xie et al[25] found in a mouse model that disruption and inactivation of PP2A (protein phosphatase 2A) facilitated downstream AKT and ERK phosphorylation, leading to migration and proliferation of HemECs. The (pro)renin receptor (PRR) is a transmembrane protein that is also an important component of RAS and associated with intercellular communication, cell proliferation, and organ development.[26] It has been shown that PRR stimulates the proliferation of HemECs through the Wnt signaling pathway.[27] NDRG1 (N-myc downstream-regulated gene 1) is a downstream regulatory gene of mTOR complex 2 (RICTOR), which plays a unique role in aerobic glycolysis by regulating glycolytic genes. It is highly expressed in ECs of IH in proliferating phase and is reduced in the involuting phase. The elevated phosphorylation level of RICTOR suggests its role in the proliferation of ECs.[28] Interleukin 6 triggers the transcriptional activity of HIF-1α in HemECs to induce the increase in the expression of VEGF-A and promote the proliferation and migration of HemECs, and activation of STAT3 is involved in this process.[29] Inhibitor of differentiation 1 (ID-1) is an oncogene for many cancers and impacts cell differentiation, tumor growth, and angiogenesis. It was found upregulated in hemangioma-derived ECs, and ID-1 stimulates HemEC proliferation by activating PI3K/AKT/mTOR signaling.[30] Although these molecules promote different target signals for HemEC proliferation and migration, the signal pathways that they influence may cross at a common point. Blocking these signal pathways at this intersection may lead to better therapeutic effects, and this intersection requires more further research.

In recent years, the role of miRNA in IH has attracted more and more attention from scholars. The expression of miR-130a is elevated in IH tissues. Inhibition of miR-130a suppresses the activation of FAK/PI3K/Rac1/mdm2 signaling, and HemECs viability declined.[31] This result suggests that miRNA-130a promotes HemEC proliferation by enhancing FAK/PI3K/Rac1/mdm2 signal transduction. miR-15a and miR-205 are upregulated and downregulated in IH tissues, respectively. At the same time, they stimulate the proliferation and cell viability of HemECs by negatively regulating AKT3 and AKT1, respectively.[18] miR-501 motivates proliferation, migration, and invasion of HemECs by targeting and inhibiting the expression of the coding sequence-specific transcription factor HOXD10.[32] There may be other miRNAs in the pathological process of IH that are not identified yet; thus, understanding their mechanism of how to effect the progress of IH may lead to new therapeutic target for IH. Long noncoding RNA is involved in a variety of physiological and pathological processes in cells, including growth and differentiation, and stress responses.[33,34] lncRNA SNHG16,[33] lncRNA OIP5-AS1,[35] and lncRNA OIP5-AS1[36,37] are upregulated in a variety of cancers and are considered as carcinogenic factors, and the expression of lncRNA SNHG16 and lncRNA CASC9 is measured in hemangioma tissues, regressive hemangioma tissues, and normal tissues, respectively. It is found that lncRNA SNHG16, CASC9, and OIP5-AS1 are significantly higher in the proliferation phase than in the other 2 groups.[33,38,39] This suggests that lncRNA SNHG16, CASC9, and OIP5-AS1 play important roles in hemangiomas. Further studies have found that lncRNA SNHG16 positively regulates STAT3 expression by binding to miR-520d-3p in HemECs, leading to proliferation and migration of HemECs.[33] CASC9 promotes proliferation, migration, and invasion of HemECs by modulating the miR-125a-3p/Nrg1 axis.[38] OIP5-AS1 irritates the proliferation of ECs by blocking the negative regulation of miR-195-5p on NOB1 and promoting NOB1 expression.[39] Reducing the expression of these 3 lncRNAs during the proliferative phase of IH can inhibit the growth of the lesion and accelerate the regression of IH.

Inhibition of Proliferation of HemECs in IH

Basic fibroblast growth factor is one of the most important growth factors in angiogenesis. Basic fibroblast growth factor exerts its function through binds to FGFR1 (fibroblast growth factor R1) on the surface of target cells to induce autophosphorylation. It plays a role in many signal transduction pathways, such as cell proliferation, differentiation, and angiogenesis.[40,41] The expression of pigment epithelium–derived factor (PEDF) is upregulated in the involuting phase of IH and can inhibit the proliferation of ECs.[42] Suggesting an increased level of PEDF during the proliferating period may expedite IH entering the involuting period.

The expression of miR-424 in the proliferating phase of IH is lower than the involuting phase, and overexpression of miR-424 suppresses the proliferation and migration of HemECs by targeting FGFR1 to inhibit the signal pathway of basic fibroblast growth factor/FGFR1, which results in the downregulation of ERK1/2 phosphorylation level.[43] Chen et al[19] have found that miR-29a, miRNA-206, and miRNA-455 expressed differently at different stages of IH. They believed that miRNA-206 played a role in the regression of IH by regulating the proliferation and migration of HemECs, but the specific mechanism was unclear.

The expression of lncRNA MEG3 is downregulated during the proliferating phase of hemangiomas. lncRNA MEG3 sponge miR-494 activates PTEN, leading to the inactivation of PI3K/AKT pathway and downregulating the expression of cycinD1 and VEGF to inhibit the proliferation of hemangioma cells.[44] Silencing of lncRNA UCA1 upregulates miR-200c expression, leading to inhibition of mTOR, AMPK, and Wnt/β-catenin signaling, thereby repressing the proliferation, migration, and invasion of HemECs.[45] Forkhead box transcription factor O1 (FOXO1) has 4 functional domains and influences basics of numerous diseases including cell proliferation inhibition, apoptosis, metabolic dysregulation, and so on. It can triggers tumor inhibition, expedite metabolic dysregulation, and mediate immune system.[46] The lack of FOXO1 in HemECs stimulates the proliferation of ECs, and the level of FOXO1 is higher in IH involuting period than in proliferating period,[28] which indicates that FOXO1 can inhibit the proliferation of HemECs.

These studies have proved the potential clinical therapeutic targets that can be used in the proliferative period of IH, through blocking

TABLE 2. Molecules Affecting HemSC Differentiation

Differentiation Direction	Related Molecules	Target Signal
HemEC	Notch4	Notch
	VEGF-B, VEGF-A	ERK1/2
Adipocyte	TBX2	C/EBPβ
	IGF-1	IGF-1R-PI3K
	IGF-2	IGF-1R-PI3K
	PPARγ2	PPARγ
Pericyte	Jagged1	Notch

the proliferation of ECs, preventing the lesions from expanding, and would be used to combine drug treatments that affect other pathways, leading to more effective treatment.

Apoptosis of HemECs in IH

Apoptosis of HemECs affects the process of IH. The apoptotic rate of ECs decreases and angiogenesis increases in the proliferating phase of IH but inverse during the involuting phase. Therefore, promoting apoptosis of ECs accelerates the regression of IH.

Proliferating cell nuclear antigen (PCNA) is essential for cell proliferation, and inhibition of PCNA expression by blocking AKT/mTOR signaling pathway simultaneously promotes apoptosis and suppresses proliferation of HemECs.[47] However, how the AKT/mTOR signaling pathway regulates PCNA is still unclear. Insulin-like growth factor II (IGF-II)/IGF2R and PCNA expression are positively correlated in IH. Knocking down IGF2R, leading to downregulation of PCNA and Bcl-2 protein, and PI3K and AKT protein activities also decrease significantly.[48] This indicates that IGF2R knockdown by blocking HemECs PI3K/AKT signal transduction to repress the expression of Bcl-2 and PCNA and facilitate apoptosis of HemECs. It has been mentioned previously in this review that upregulation of ID-1 promotes the proliferation of HemECs and inhibition of ID-1 expression induces apoptosis of HemECs via PI3K/AKT/mTOR signaling inactivation.[30] The previous studies indicate that PI3K/AKT signaling pathway plays an important role in the survival and proliferation of HemECs.

Vascular endothelial growth factor and its receptors not only affect the proliferation of HemECs but also promote the survival of HemECs. Upregulation of VEGF/VEGFR-2 expression activates PI3K/AKT signaling and promotes the elevation of the antiapoptotic protein Bcl-2, thereby inhibiting apoptosis of HemECs.[49] Suppression of VEGF-A can significantly facilitate the rise of proapoptotic proteins CYTC and caspase-3 and decrease the level of antiapoptotic protein Bcl-2. Inhibition of VEGF-C can significantly promote the level of proapoptotic protein caspase-9 and reduce the level of Bcl-2.[14] This indicates that VEGF-A and VEGF-C have signal overlap during the regulation of HemEC survival. LncRNA NEAT1 reduces the apoptosis of HemECs by targeting inhibition of miR-361-5p to positive regulation of VEGFA expression.[50] linc00152 is upregulated in HemECs, and knockdown of linc00152 can simultaneously inhibit AKT/mTOR and Notch1 signaling pathways, leading to apoptosis of HemECs.[50] As noticed from the previously mentioned statements, both various molecules and lncRNA affect the survival of HemECs through PI3K/AKT signal transduction. Thus, inactivation of PI3K/AKT signal pathway not only inhibits the proliferation of HemECs but also promotes HemEC apoptosis, indicating an excellent therapeutic target for IH.

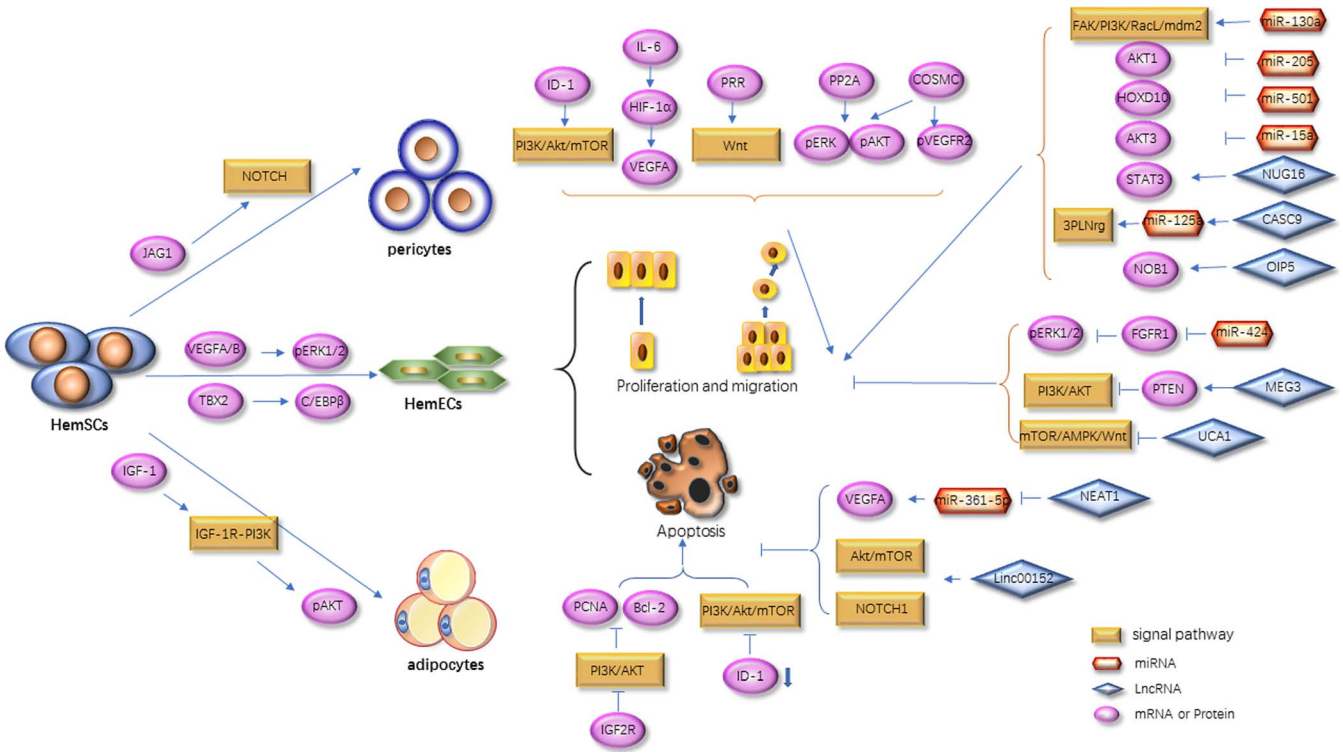

FIGURE 1. Summary diagram of molecular mechanism. p, phosphorylation. In the proliferative phase of IHs, HemSCs mainly differentiate into ECs, ECs proliferation and migration are enhanced, apoptosis is decreased, and ECs promote differentiation of HemSCs into pericytes. In the involuting phase, HemSCs are mainly differentiated into adipocytes. In addition, proliferation and migration of HemECs are inhibited and apoptosis is enhanced. AKT signaling pathway plays an important role in the proliferation, migration, and apoptosis of HemECs. full color online

Hemangioma SCs in IH

Stem cells take shape of new blood vessels called vasculogenesis, which is another major source of blood vessels in IH. Hemangioma stem cells differentiated into HemECs to induce angiogenesis. Together, they facilitate the expansion of IH's lesions.[16,51]

Many studies have isolated and identified HemSCs from IH tissues, established mouse models,[8,52] and studied the effects of some molecules on their differentiation. Hemangioma stem cell–induced IH model in mice can re-enact the process of hemangioma development in humans. Therefore, HemSCs that specifically express CD133 cause the onset of IH.[53] During the proliferating period of IH, HemSCs mainly differentiated into HemECs and pericytes, which lead to the rapid production of vascular. In the involuting phase, HemSCs mainly differentiated into fat cells and promoted the regression of IH. Studying the effects of these molecules on their differentiation will help develop new drugs for the treatment of IH. Corticosteroids treat IH by silencing the expression of VEGF-A in HemSCs to suppress vasculogenesis.[54] β-Adrenergic blocker propranolol has been used as the first-line drug for the treatment of IH. One of its mechanisms is to accelerate the differentiation of HemSCs into adipocytes.[55] The key molecules that involved in the differentiation of HemSCs were listed in Table 2.

Differentiation of HemSCs into HemECs

Hemangioma ECs are mainly derived from the differentiation of HemSCs. Several studies investigated the effect of signaling pathways implicated in EC differentiation.[53,56,57] The Notch signal regulates the communication of cell-to-cell, which has been shown to play an important role in survival, differentiation of various stem cells, vasculognesis, and angiogenesis.[58,59] It has 4 receptors, Notch1, Notch2, Notch3, and Notch4.[56] Notch1/4 are highly expressed in HemECs and HemSCs, and the expression of Notch1/4 in HemECs is higher than that in HemSCs. However, Notch3 is not detected in the EC in HemECs.[57] It is suggested that the differentiation of HemSCs into HemECs is related to the expression of Notch1/4, which can be verified by knocking down Notch 1/4 in HemSCs. Notch2 and Notch3 may induce differentiation of HemSCs in other directions. This also indicates the vital role of NOCH signals in the development of IH.

Human VEGF-A and VEGF-B expedite HemSC differentiation into HemECs by strongly inducing phosphorylation of ERK1/2 in HemSCs.[53] Thus, inactive ERK1/2 or Notch4 signals may be a therapeutic strategy to accelerate IH regression, but how the Notch4 signal stimulates HemSC differentiation into HemEC still needs to be illuminated.

Differentiation of HemSCs Into Adipocytes

During the involuting phase of hemangioma, the lesion is gradually filled with adipose and fibrous tissues.[5] If HemSCs are facilitated to differentiate into adipocytes, it will accelerate IH from the proliferating phase to the involuting phase. Transcription factor T-box2 (TBX2) can control cell-fate decisions,[60] and it is found to be highly expressed in HemSCs. Transcription factor T-box2 regulates adipogenesis in HemSCs, and overexpression of TBX2 stimulates the differentiation of HemSCs into adipocytes, by promoting the expression of early transcription factors C/EBPβ.[2] Insulin-like growth factor 1 (IGF-1) functions by binding to its receptor IGF-1R, which belongs to tyrosine kinase family of growth factor receptors. Insulin-like growth factor 1R has 2 extracellular α-subunits and 2 membrane-spanning β-subunits to form an intracellular tyrosine kinase.[61] Insulin-like growth factor 1 is necessary for mitogenic, differentiation responses, and anabolic in myocardium and skeletal muscle. In the meantime, it affects the progression of multicancers.[61] Insulin-like growth factor 1 upregulates phosphorylation of AKT by regulating IGF-1R-PI3K signaling pathway, which does not only expedite the proliferation of HemSCs but also stimulate the differentiation of HemSCs into adipocytes.[62] Insulin-like growth factor 2 has been proven to play the same role as IGF-1 in HemSCs and has the same mechanism of action,[63] but Kleiman et al[64] found that the ability of leptin to induce differentiation into adipose in HemSCs was inhibited by elevating IGF-2. This requires more in-depth research to demonstrate the specific role of IGF-2 in HemSCs and its mechanisms. Yuan et al[65] have shown that overexpression of the late transcription factors PPARγ2 can promote the differentiation of hemangioma mesenchymal stem cells into adipocytes, and it may promote the differentiation of HemSCs into adipocytes. Insulin-like growth factor 1 is a kind of polypeptide that expresses in various tissues to promote adipogenesis.[66] These studies are expected to provide a new therapeutic approach for HemSCs to differentiate into adipocytes in the proliferating phase of IH.

Differentiation of HemSCs Into Pericytes

Pericytes are widely present around IH blood vessels, which are mainly differentiated by HemSCs.[67] Notch ligand Jagged1 (JAG1) is a ligand of the Notch family and is highly expressed in HemECs.[68] It consists of 3 parts, a small intracellular domain, a larger extracellular, and a transmembrane domain. Jagged1 expresses in multitudinous tissues of the human body and is essential for development of various organs. It is closely interrelated to the occurrence of diversiform diseases. Jagged1 mutation causes alagille syndrome, and JAG1 missense mutations were detected in patients with tetralogy of Fallot and pulmonary stenosis. It is also implicated in multifold cancer and cancerous biology, such as neoplastic cell growth, metabolism, and angiogenesis. Jagged1 plays an essential role during differentiation of HemSCs into pericytes. Jagged1-expressing fibroblasts can induce differentiation of HemSC into pericytes.[67] However, there are few studies on the mechanism of function of Jagged1 in IH, but Jagged1 accelerates angiogenesis and affects the progression of IH by facilitating differentiation of HemSCs into pericytes.

DISCUSSION

Infantile hemangioma is the most common benign tumor in children, and its specific pathogenesis is still unclear. Current research proves that HemSCs play an important role in the pathogenesis of IH. Most of the studies have focused on the factors affecting the proliferation and apoptosis of HemECs, but there are few studies on the differentiation of HemSCs. HemECs can only be regarded as symptoms of microscopic disease in IH, not the cause of disease. Of course, reducing HemECs can promote the regression of IH but cannot prevent or reduce the occurrence of IH, and it is necessary to clarify the cause of the disease. Although there are many methods for the treatment of IH in clinical practice, none of them are perfect. In the treatment, drugs that promote the differentiation of HemSCs into adipocytes can be developed, so that the growth of IH can be inhibited in time before the lesion is enlarged. Here, we summarize the molecules that have been studied to influence the progression of IH, to let scholars who are new to this research direction understand the state of research in this field and to lay the foundation for subsequent research. According to current research, IHs are caused by a variety of factors. In the future, it may be possible to develop treatments that promote the differentiation of HemSCs into adipocytes, can inhibit the increase of HemECs at the same time, and promote the apoptosis of HemECs. There are still many restrictions in our analysis. For example, there are still few studies on infant and hemangiomas, and its pathogenesis has not been clarified, few studies affecting the differentiation of HemSCs into pericytes, so a lot of work is still needed in the future.

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