[Frontiers in Bioscience, Landmark, 20, 1004-1016, June 1, 2015]

Infantile haemangioma: a complicated disease

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1. ABSTRACT

Infantile haemangiomas (IH) are common benign vascular tumors of childhood. They are characterised by rapid growth during the first year of life and slow regression that is usually completed by 7–10 years of age. The underlying mechanism of action of IH is aberrant angiogenesis and vasculogenesis, and involves the mammalian target of rapamycin pathway and vascular endothelial growth factor pathway. IH become a challenge if they are part of a syndrome, are located in certain areas of the body, or if complications develop. The beta-adrenergic receptor blocker propranolol is a promising new candidate for first-line systemic therapy. This review focuses on the clinical characteristics, pathogenesis and management of IH.

2. INTRODUCTION

Infantile haemangioma (IH) is a benign (non-cancerous) condition affecting cutaneous blood vessels (1, 2). It is also termed “proliferative haemangioma” because it is due to proliferating endothelial cells (cells that line blood vessels). IH (as distinct from vascular malformations at birth) are proliferative lesions that usually develop shortly after birth (3-6). About 80% of IH occur on the head and neck area (7). They grow to 80% of maximum size in the first three months and most stop growing at about five months. However, they may keep growing for ≤18 months (8). Nearly all flat IH eventually involute and disappear without treatment. However, regression of bulky IH tends to be incomplete, and they may leave an irregular atrophic (thin) scar or anetoderma (dented scar) in ≥50% of cases (9).

In some respects, IH appear to be the product of disorganised and rapid growth of blood vessels. In fact, angiogenesis and vasculogenesis have been considered to be mechanisms contributing to the neovascularisation in IH (10, 11). Angiogenesis is characterised by the growth of new vessels from pre-existing vessels. This phenomenon requires degradation of the basement membrane, migration of endothelial cells and tubulogenesis, followed by recruitment of perivascular cells (12-14). Vasculogenesis is the *de novo* formation of blood vessels from stem cells or progenitor cells (11, 15, 16).

In the past decade, several of the "building blocks", the cells comprising the IH, have been isolated. Among these building blocks are IH progenitor/stem cells, endothelial cells, and pericytes (17). Various factors have been identified to be involved in IH development: the angiogenesis-related receptors E-selectin, integrin αvβ3 and integrin α5β1; basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF); and insulin-like growth factor -2 (17). The pathogenesis of IH is complicated and includes proliferation and involution phases, which are controlled by numerous potential regulators at various levels and include molecular, cellular, and hormonal changes (18). The mechanism that initiates involution of IH is not clear, but is associated with an increase in the number of mast cells as well as a fivefold increase in the number of apoptotic cells (one-third of which are endothelial cells) (18). This review will focus on the pathogenesis, molecular mechanism, and treatment of IH.

3. EPIDEMIOLOGY OF IH

IH are characterised by early growth after birth related to cellular (mainly endothelial) hyperplasia, and are the most common benign tumors of childhood. Absence of a tracking mechanism has limited epidemiological data. IH have been estimated to occur in 3–10% of Caucasian infants, developing during the first weeks of life, usually until 3–6 months of age and then involuting very slowly over 3–7 years (19, 20). However, the exact prevalence of IH remains difficult to ascertain (21). In most cases, these vascular tumors are difficult to detect at birth (present in ≈1–2% of newborns), with lesions becoming apparent during the first few weeks or months of life. Therefore, IH are not documented in state birth-defect registries (4, 22).

Risk factors accounting for the development of IH have been identified (23, 24). It has been reported that girls are more likely to develop IH with a sex ratio ranging from 3:1 to 5:1 and even to 9:1 in the case of abnormalities such as posterior fossa malformations–hemangiomas–arterial anomalies–cardiac defects–eye abnormalities–sternal cleft and supraumbilical raphe syndrome (PHACES syndrome) (25), which is a cutaneous condition characterised by multiple congenital abnormalities (23, 24). This information suggests that the estrogen signaling pathway may be involved in IH. Other identified risk factors include: family history of IH; prematurity; race (Caucasian); low birth weight (<1500 g); and newborns from multiparous women (22). In particular, infants from women who have undergone chorionic villus sampling may also be at increased risk for developing IH.

4. CLINICAL CHARACTERISTICS OF IH

IH are the most common benign vascular tumours in infancy, occurring in ≈4–5% of the population. IH have predictable growth characteristics. Better understanding of the feature of IH is important for anticipatory guidance for parents and planning management (26).

4.1. Natural history of IH

At birth, IH are absent or present as precursor lesions. Premonitory symptoms usually comprise a vasoconstricted patch, a bruise-like macule, or an erythematous telangiectatic patch (27-29). Most IH follow a sequential lifecycle that begins with a rapid proliferative phase lasting ≈6 months followed by continued slower growth during the first year of life. Specifically, there is often an early proliferative phase characterised by rapid growth after birth. The most rapid growth of IH occurs between 5.5. weeks to 7.5. weeks of age (28, 29). A long-appreciated characteristic of IH growth is its tendency to "mark out" its territory early, with growth proceeding volumetrically rather than radially (8). In proliferative phase, IH stem cell may serve as progenitors and begin dividing under appropriate conditions (Figure 1). Prospective cohort studies have helped describe more precisely the proliferative phase demonstrating that, irrespective of subtype or depth, IH reach 80% of their final size by 3 months of age (8). After the early proliferative phase, a period of slower growth, called the late proliferative phase, occurs until age 6–9 months (30). During this growth phase, 80% of IH double their original size, 5% triple their original size, and <5% dramatically extend until involving a functional, vital or aesthetic prognosis (31). The proliferative phase is followed by involution that takes place over years. The involution phase appears to be a more quiescent or '*plateau*' phase in which cellular proliferation and apoptosis offset each other (32). If cell death outpaces proliferation, this marks the transition to a longer period of involution that can last from months to years: 10% of IH regress completely at 1 year of age, 50% by 5 years of age, and 70% by 7 years. After involution, some patients are left with an area of redundant cutaneous and/or fibrofatty tissue, whereas others manifest a central area of thin, parchment-like tissue, sometimes with superimposed telangiectasia (32) (Figure 1).

4.2. Histopathology of IH

Histopathological evaluation of IH tissue reveals findings dependent on the phase of the IH lifecycle (33). Early proliferating lesions show compact areas of uniform endothelial cells arranged in cords and nodules. Endothelial-cell-lined lumina, if present, are subtle in early lesions, but become more apparent in lesions at later points in development, often displaying thickened, multilaminated basement membranes. In older, involuting lesions, the lumina become narrower, and fibrofatty tissue is often observed (32).

4.3. Clinical types of IH

Several clinical types of IH have been categorised based on certain morphological characteristics (34, 35).

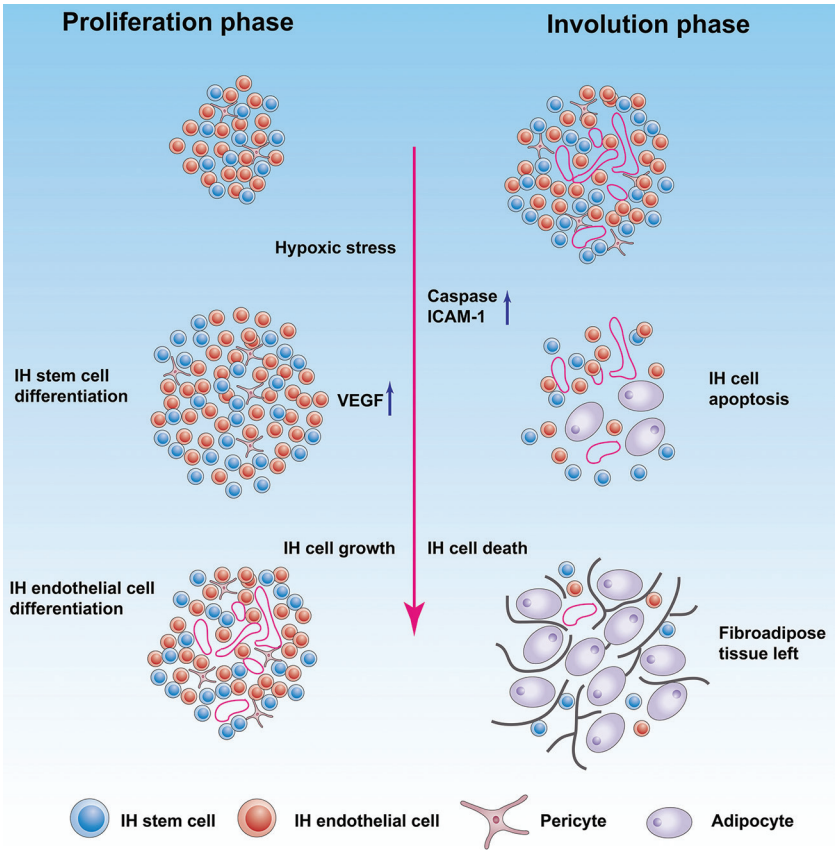

Figure 1. Natural history of IH. In proliferative phase, IH stem cell under the influence of unusual conditions such as hypoxic stress may serve as progenitors and begin dividing under appropriate conditions. The growing tumors comprise IH endothelial cells and pericytes. The early lesion is largely a featureless mass of cells, but sometime later in the proliferative phase, lumenised capillary-like structures are organised. Cell apoptosis and the regression of both the endothelial and nonendothelial compartments occur in the involution phase. After involution, adipocytes may be found at the site along with a fibrous matrix.

Superficial IH (50–60%) correspond to a 'strawberry' IH that present as a bright-red tumours with irregular hummocky surfaces edged in relief and surrounding normal teguments. Subcutaneous IH (≈15%) are often described as swollen, protruding, rounded and warm under normal or bluish skin. Mixed IH (≈25–35%) are a combination of primary superficial components associated with later deep subcutaneous extensions. Whatever the clinical type, IH have firm and elastic textures, slightly warm to the touch, not pulsatile and usually painless, except in cases of ulceration (22, 36).

4.4. Location and size of IH

IH seem to be more frequently located on the face (40%) and neck (20%). However, for reasons that remain unknown, they may affect any other region of the body, including internal organs (37). In addition, the distribution of facial IH is not random, with 76% of IH located on bony prominences and 60% concentrated in the centro-facial area (a region that accounts for only 20% of the entire facial area) (38, 39). One plausible hypothesis is that pressure points that correspond to hypoxic areas (especially in cases of cephalic presentation at delivery) may influence the localization of IH (40). The size of an IH may vary greatly, ranging from a pinhead to involvement of an entire limb or hemi-trunk. However, 80% of IH are <3 cm (41). With regard to giant forms, two distinct forms should be considered depending on the existence of a clinically observable precursor lesion. Therefore, the presence of an anaemic macule at birth is associated with a secondary apparition of IH that spreads to the surface. Conversely, the development of an IH on uninvolved skin is associated with a combination of subcutaneous spread and skin spread (22).

5. PATHOGENESIS OF IH

The pathogenesis of IH remains poorly understood (42, 43). A universal consensus is lacking, but several hypotheses regarding the aetiology of IH have emerged, and some have gained significant support (44, 45). The concept that IH arises from a dysregulation of IH cells has been considered for several decades. Many scholars believe that abnormal IH cells contribute to the neovascularisation in IH by angiogenesis and vasculogenesis (17, 18, 46).

5.1. Characteristics of IH cells

IH is a complex mixture of cells, including a small proportion of multipotent stem cells (cluster of differentiation 133^+, $CD133^+$) and a majority of immature endothelial cells ($CD31^+$), pericytes (smooth muscle $actin^+$, SMA^+), dendritic cells (factor $XIIIa^+$) and mesenchymal cells with adipogenic potential (47). Mast cells and myeloid cells may also be recruited within the tumor.

In the last decade, several research teams have isolated a primitive mesenchymal cell with these properties from proliferating phase IH using marker CD133 (a glycoprotein on cell-surface membrane expressed on many types of human stem cells and progenitor cells) (47-49). $CD133^+$ cells comprise 0.1.–1% of the cells in the proliferating phase of IH. $CD133^+$ cells in IH, called haemangioma stem cells, appear to self-renew and undergo multi-lineage differentiation (47). Haemangioma stem cells form vessels *de novo* strongly to induce vasculogenesis, which may be the underlying mechanism of the genesis of IH (50, 51).

Mulliken *et al*. have shown that IH-derived endothelial cells proliferate readily and exhibit angiogenesis *in vitro* (i.e., form capillary-like tubes in culture dishes) (52). Endothelial cells are considered to proliferate rapidly. During the growth phase of IH, endothelial and interstitial cells strongly express a marker of proliferation: MIB 1 (53, 54). Furthermore, $CD31^+$ endothelial cells are clonal and express a particular phenotype: indoleamine 2,3 dioxygenase (IDO), lymphatic vessel endothelial hyaluronan receptor 1 (LYVE-1), merosin, chemokine (C-C motif) receptor (CCR) 6, glucose transporter (GLUT)-1, antigen Lewis Y (Ley) and antigen FcRcII, CD15. IDO and LYVE-1 are all positive in the early phase of IH and become further negative once they mature to become almost normal endothelial cells with slight expression of GLUT-1, Ley, FcRcII and merosin-markers (53, 54). These latter markers are positive in the three phases of IH evolution, whereas they are absent in other tumours and vascular malformations (55). Additionally, during the involution phase, endothelial cells express caspases, which are markers of apoptosis (56). This could explain the augmented apoptosis in the involution phase of IH.

The perivascular cells surrounding the nascent vessels in the proliferative phase express the pericyte markers α-SMA, neural glial antigen-2 (NG2), platelet-derived growth factor receptor-β (PDGFRβ), calponin, and smooth muscle myosin heavy chain (57, 58). It has been shown that pericytes can be isolated from the proliferating phase and involuting phase of IH specimens from different patients (59). Further investigation found that pericytes are abundant in the proliferating phase and appear to undergo maturation concurrently with endothelial cells. *In vitro*, IH-derived pericytes were found to express all of the markers detected in cells surrounding IH vessels in histological sections (including NG-2, PDGFRβ, calponin, α-SMA, and NOTCH3) consistently over several passages *in vitro* (59). When IH pericytes were combined with endothelial cells and implanted in mice, cells assembled into vessels that connected with murine vessels within 7 days. When compared with normal human pericytes isolated from the retina or placenta, IH pericytes proliferated more rapidly, expressed more VEGF-A, but expressed reduced levels of angiopoietin-1 (ANGPT1). In co-culture, IH pericytes showed a reduced ability to suppress the proliferation and migration of normal human endothelial cells (59). Taken together, IH pericytes exhibit certain characteristics: increased expression of VEGF-A; decreased expression of ANGPT1; increased proliferation; increased vessel formation *in vivo*; and a decreased ability to suppress the proliferation and migration of endothelial cells, suggesting that IH pericytes are pro-angiogenic.

Mast cells and myeloid cells have also been found to be recruited within IH (60-64). The number of mast cells predominates in the early-to-middle involuting phase, whereas lower numbers are seen in the proliferative and involuted phases (60, 63). Collectively, IH contain several cell populations that affect IH development in different ways. However, the underlying mechanisms need further clarification.

5.2. Angiogenesis and vasculogenesis in IH

Normal blood vessels typically arise from one of two processes: angiogenesis or vasculogenesis. Angiogenesis is the physiological process through which new blood vessels extend and remodel from pre-existing vessels (12-14). This is distinct from vasculogenesis, which is the *de novo* formation of endothelial cells from precursors of mesoderm cells (11, 15, 16). The first vessels in the developing embryo form through vasculogenesis, after which angiogenesis is responsible for most (if not all) growth of blood vessels during development and in disease. Angiogenesis is a normal and vital process in growth, development, wound healing and formation of granulation tissue (12-14). However, it is also a fundamental step in the transition of tumours from benign to malignant ones, leading to the use of angiogenesis inhibitors in the treatment of cancer.

The first endothelial structures to form in the embryo are examples of vasculogenesis (65). The cells of these endothelial structures originate from mesoderm-derived haemangioblasts, which are believed to function as progenitors to haematopoietic and endothelial cells (66). This is relevant to understanding IH pathophysiology because endothelial cells from IH co-express haematopoietic and endothelial-cell markers. Angiogenesis is active later in blood-vessel development and occurs in the normal adult under certain conditions (e.g., the endometrium during the female reproductive

cycle) (67, 68). Angiogenesis plays an important part in many pathological conditions: growth of solid tumors, arthritis, and eye diseases. Some aspects of angiogenesis and/or vasculogenesis are probably involved in the growth of IH, but the growth of these tumours differs in several important ways from typical angiogenesis or vasculogenesis (14).

Disorganised and rapid growth of blood vessels could contribute to IH occurrence, so angiogenesis and vasculogenesis processes may be involved in the neovascularisation of IH (10, 69). There are several similarities between normal blood vessels and the structures found in IH. Briefly, IH primarily comprise endothelial cells possessing components of a basement membrane (e.g., type-IV collagen, associated pericytes). During the proliferation phase, normal endothelial cells and IH endothelial cells express the angiogenesis-related receptors E-selectin, integrin αvβ3 and integrin α5β1. Many other factors previously found to be associated with normal angiogenesis have also been reported to be expressed in IH, such as bFGF (70, 71).

5.3. Molecular basis of IH

5.3.1. VEGF signaling pathway

The VEGF signaling pathway is the key pathway of the several signaling routes linked with IH pathogenesis (72). VEGF-A is a master regulator of angiogenesis and vasculogenesis (73, 74). VEGF-A appears to be at higher levels in the proliferating phase compared with the involuting phase of IH, and its level in the serum of IH patients is decreased after systemic corticosteroid therapy (75). Increased stabilisation of hypoxia inducible factor-1α (HIF-1α) was found in patients with proliferating IH, suggesting that the high expression of VEGF might be related to hypoxia (76). Recently, it has been found that corticosteroids (the mainstay of treatment of IH) dramatically down-regulate VEGF-A secretion by IH stem cells (77). Furthermore, knock-down of the expression of VEGF-A or VEGF receptor 1 (VEGFR-1) in IH stem cells by short-hairpin RNA was sufficient to block blood-vessel formation *in vivo*. In contrast, IH endothelial cells express and secrete very little VEGF, and these low levels are not affected by corticosteroid treatment (78).

VEGFR-1, VEGFR-2 and VEGFR-3 are the receptors of VEGF-A. VEGFR-2 has been found to mediate almost all of the known angiogenic responses to VEGF-A. In contrast, the function and signaling of VEGFR-1 (which is present on endothelial and non-endothelial cells) is less understood. VEGFR-1 is considered to be a “VEGF-A trap” due to its high binding affinity for VEGF and its relatively low kinase activity. IH endothelial cells, as well as IH specimens, express relatively low levels of VEGFR-1. Low expression of VEGFR-1 results in increased VEGF-dependent activation of VEGFR-2 and downstream signaling pathways (79, 80). In conclusion, several investigations have identified the critical role for VEGF and its receptors in the vasculogenesis and angiogenesis in IH.

5.3.2. ANGPT and TIE2

ANGPT is part of a family of vascular growth factors that play a part in embryonic and postnatal angiogenesis (81). ANGPT signaling most directly corresponds with angiogenesis (the process by which new arteries and veins form from pre-existing blood cells) (82). ANGPT1 is critical for the maturation, adhesion, migration, and survival of vessels. ANGPT2 promotes cell death and disrupts vascularisation (83). ANGPT1 and ANGPT2 signal through the endothelial membrane receptor TIE2 to regulate distinct steps in the remodeling and maturation of vessels (84). It has been shown that IH cells exhibit higher expression of the ANGPT1 receptor TIE2 and have increased responses to ANGPT1, whereas expression of ANGPT2 mRNA was down-regulated in response to serum containing endothelial cells from IH but not from normal endothelial cells (85, 86). Further investigations are needed to ascertain the role of ANGPT and TIE2 in the growth and involution of IH.

5.3.3. Mammalian target of rapamycin (mTOR) pathway

mTOR is a serine/threonine protein kinase and member of the phosphatidylinositol 3-kinase-related kinase family (87). The protein consists of a catalytic kinase domain, a FKBP12-rapamycin binding domain, a putative auto-inhibitory domain (repressor domain) near the C-terminus and ≤20 tandemly repeated HEAT motifs at the amino terminus, as well as FAT (FRAP-ATM-TRRAP) and FATC (FAT C-terminus) domains. mTOR is a major intersection that translates signals from the extracellular *milieu* (e.g., glucose, amino acids, growth factors), and functions as a central element in a signaling pathway involved in the control of the growth and proliferation of cells (87). The mTOR inhibitor rapamycin is known to have an anti-angiogenic effect on endothelial cells in pathological settings, and has shown efficacy in the treatment of complicated vascular malformations (88). Rapamycin inhibits the proliferation and self-renewal activity of IH stem cells, thereby preventing IH stem cells, alone or combined with endothelial cells, from forming blood vessels *in vivo* (89). Besides its anti-vasculogenic effect on IH stem cells, rapamycin has anti-angiogenic effects on IH endothelial cells, suppressing their proliferation and leading to regression of pre-existing IH (90). These observations suggest that the mTOR signaling pathway play have a critical role in IH development.

Notch, monocyte chemotactic protein 1, interleukin-6, urokinase receptor, and insulin-like growth factor-2 have been found to be expressed differentially in the proliferating phase of IH (17). However, their role in IH development requires identification. The SKI oncogene

(a transcriptional repressor that inhibits expression of transforming growth factor (TGF) β family members) was found to be highly expressed in the endothelium of proliferating-phase IH, but was not detected in several specimens of vascular malformation, suggesting that TGFβ signaling may be suppressed in IH (91). The cell-adhesion molecule E-selectin, normally expressed only in the inflamed endothelium, is strongly expressed on vessels in proliferating-phase IH. E-selectin is also constitutively expressed by proliferating-phase IH endothelial cells, and appears to mediate interactions with IH stem cells (92, 93).

6. TREATMENT OF IH

IH treatment has a long history (94). From 1930 to 1950, X-ray therapy was an effective treatment for IH. However, apart from the fact that patients were exposed to radiation, X-ray therapy was associated with late sequelae such as atrophy, contractures, pigmentation and telangiectasia (95). From the 1950s, a watch-and-wait approach was applied given the natural course of IH. In the mid-1960s, systemic corticosteroids were found to be effective treatment (96). In 1989, laser therapy was developed, and the pulsed-dye laser became another potential treatment for IH. It was effective in very superficial lesions and can help accelerate healing in some ulcerated IH (97). Management and therapy of IH have changed considerably since 2008. In 2008 Léauté-Labrèze *et al*. reported that IH had regressed with orally administered propranolol (98). Propranolol soon became the first-choice treatment of IH.

Management of IH comprises topical therapy or systemic therapy (94). In general, topical agents are supposed to be used for small, superficial and localised IH or during early proliferation, when it may not be possible to determine if a deeper component is needed. Systemic therapy is reserved for larger IH, those with more aggressive growth characteristics or high threat of functional impairment, and those not responding to local measures where treatment is deemed necessary (94).

6.1. Topical therapy

A variety of topical agents have been proposed for use in IH. Several studies have supported the efficacy of timolol maleate (0.5.% solution) for treatment of small and/or superficial IH since the first report in 2010 (99, 100). The gel-forming solution vehicle is preferred for IH treatment because it has less systemic bioavailability than the solution form. Theoretical complications may include hypoglycaemia hypotension wheezing and bradycardia secondary to systemic absorption. However, such complications have not been reported in infants treated for IH. In addition, intralesional corticosteroids have a useful role as local treatment for selected cases, particularly for early, localised IH of the lip or nasal tip. Intralesional corticosteroids may stabilise growth or decrease the size of the IH, thereby helping to avoid systemic therapy or surgery (101).

6.2. Systemic therapies

For a long time, corticosteroids were the first option for IH treatment, even though really successful results were obtained in only a small proportion (≤50%) of IH (102). Corticosteroids can be administered *via* oral or intravenous routes. Adverse effects are reversible and include: increased appetite; Cushing's syndrome; behavioural changes (restlessness); increased episodes of crying; adrenal insufficiency and hypertension (103). Corticosteroids can regulate vasculogenic potential. It has been shown that dexamethasone suppresses the vasculogenic potential of IH-derived stem cells in a murine model. Furthermore, dexamethasone suppresses VEGF-A expression by IH-derived stem cells *in vitro* and silencing of VEGF-A expression inhibits the vasculogenic potential of these cells *in vivo* (102).

Propranolol, the most commonly used beta-blocker against IH, is an orthosteric antagonist of β1- and β2-adrenergic receptors. Since its efficacy in shrinking IH was first reported by Léauté-Labrèze *et al*. in 2008, propranolol has dramatically altered the treatment landscape of IH (98). Propranolol is now considered by most experts to be first-line therapy if systemic treatment is indicated. The most common serious side effects are bradycardia, hypotension, dyspnoea, congestive heart failure, hypoglycemia, nightmares and decreased cardiac output but, in fact, these are rarely related directly to propranolol use (104). Despite its widespread use, the mechanism of action of propranolol in IH treatment remains uncertain. Expressions of β-adrenergic receptors have been shown in IH. Specifically, expression of the β1 receptor is located mainly in endothelial cells, whereas the β2 adrenergic receptor is mainly found in IH endothelial cells and pericytes (105). After propranolol administration, a rapid change in the colour and consistency of the IH is observed. Therefore, it is reasonable to suggest that propranolol exerts its effect *via* vasoconstriction of the high-flow blood vessels feeding the IH. Additional mechanisms of propranolol treatment against IH might be responsible for VEGF suppression, as well as modulation of HIF-1α protein, and matrix metalloproteinases (106).

7. CONCLUSION

IH are the most common tumors of infancy. Abnormal vasculogenesis and angiogenesis regulated by several factors (e.g., VEGF, E-selectin) might be potential contributors of IH. The VEGF pathway and mTOR pathway have been shown to be involved in IH development. Most IH do not require treatment; if necessary, the initial decision is whether to treat with topical or systemic therapy. However, the underlying mechanisms of action of these treatment strategies need further investigation.

8. ACKNOWLEDGEMENT

Financial support came from the Science and Technology Commission foundation of Shanghai,China(No.13140903802),the Medicine and Engineering Cross foundation of Shanghai Jiaotong University(No.YG2012MS33).

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Abbreviations: ANGPT1, angiopoietin-1; bFGF, basic fibroblast growth factor; CCR, chemokine (C-C motif) receptor; CD, cluster of differentiation; GLUT, glucose transporter; HIF-1α, hypoxia inducible factor-1α; IDO, indoleamine 2,3 dioxygenase; IH, infantile haemangioma; Ley, antigen Lewis Y; LYVE-1, lymphatic vessel endothelial hyaluronan receptor 1; mTOR, mammalian target of rapamycin; NG2, neural glial antigen-2; PDGFRβ, platelet-derived growth factor receptor-β; SMA, smooth muscle actin; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; TGF, transforming growth factor

Key Words: Infantile Haemangioma; Benign Vascular Tumor; Clinical Treatment, Review

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