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Medical Management of Vascular Anomalies

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Abstract

Purpose of review—This chapter will summarize the most recent literature regarding the current state of medical treatment for vascular anomalies.

Recent findings—Research into the biology of these anomalies has strengthened our understanding of each anomaly and has helped to pave the way for more tailored treatment options involving molecular and/or genetic targets.

Summary—While there is still a role for surgical intervention, medical therapies that target the etiology of vascular anomalies may represent an alternative or adjunctive approach in the management of these lesions.

Keywords

Infantile hemangioma; propranolol; genetics; rapamycin; lymphatic malformation; vascular anomalies

Introduction

The study of vascular anomalies has progressed significantly through the last three decades. With more advanced diagnostic testing modalities, the characteristics that make each anomaly unique can be better described. Defining the specific features of each type of anomaly has allowed in-depth research to better elucidate genetic etiologies of these lesions. The human genome project was completed in 2003 and that information has become a valuable resource in guiding this research.[1] The importance of genomic medicine is incorporated into the vascular anomaly classification of the International Society for the Study of Vascular Anomalies' (ISSVA) (Table 1). This comprehensive list divides the larger

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group of vascular anomalies into specific variations and, when known, correlates each to the causative gene. These known genetic causes have led to the discovery of potential molecular targets for new medical therapies as well as an explanation for the efficacy of other treatments.

The most recent research exploring new medical therapeutic options for patients with infantile hemangiomas (IH), PHACES (posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects, eye abnormalities, sternal cleft and supraumbilical raphe) syndrome, lymphatic malformations (LM), venous malformations (VM) and arteriovenous malformations (AVM) is described.

Infantile Hemangiomas

Description of Disease and Complications

The most common benign tumor of childhood is infantile hemangioma (IH) and occurs in 4-10% of infants.[2,3] IH are more common in Caucasian females, prematurity and low birth weight.[4] IH are absent at birth, typically occur during infancy, rapidly proliferate after the first few months of life, and then slowly involute over the course of years. Most IH (80-85%) involute spontaneously with the loss of IH endothelium and replacement with fibrofatty tissue.[5,6]

If left untreated, IH can lead to complications based on its location and size. Growing lesions in a small infant airway can cause airway compromise. Large IH can lead to cardiac failure during rapid lesion proliferation from intralesional blood shunting directly from the arterial to venous circulation. Those involving the face can cause psychosocial developmental abnormalities, significant disfigurement depending on the location, and vision loss if there is periorbital involvement. Patients with periorbital IH should have an ophthalmologic evaluation to rule out amblyopia.[7,8] Ulceration and bleeding can also be complications to warrant prompt treatment.[8-11]

Etiology of Disease

IH endothelium are unique as compared to other endothelium as they have high expression of the glucose transport protein, GLUT-1 and a cluster of microRNA from chromosome 19 (C19MC), all of which are highly expressed in specific placental cells.[12,13] In addition to the possible placental origins of IH is the idea that IH arise from CD 133+ stem-cells.[6] One of the problems in determining stem cell origins of IH endothelium is that immunostaining IH tissue for CD 133 cells has not been reliable, so it has not been possible to delineate histologically whether GLUT-1+ IH endothelium and/or placental cells are also stem cells. Certainly, these complex cellular interactions distinguish IH clinically and biologically from other vascular anomalies even though the exact molecular mechanisms giving rise to IH are being determined.

Historic Medical Treatments

When IH were thought to result from disordered angiogenesis, interferon-alpha, the first known naturally occurring angiogenesis inhibitor, was used systemically in complicated IH

cases. It was shown to be effective in 45% of cases; however, the undesirable side effect of spastic diplegia made it an unattractive first-line therapy in young children.[14] Until 2008, corticosteroids, also angiogenesis inhibitors, were the mainstay of IH treatment. These drugs were used systemically or via intralesional injection and had variable efficacy. Long-term, high dose corticosteroids needed to treat large IH have side effects such as adrenal insufficiency, insomnia, irritability, glucose intolerance and osteoporosis.[15] Vincristine is a chemotherapeutic drug that inhibits microtubule function, arresting cell mitosis. Vincristine inconsistently improved life-threatening IH.[16-19] This inconsistent treatment response and poor safety profile makes vincristine a less popular IH therapy. The mention of these medications is of historic reference and they are no longer routinely used.

Propranolol

Discovery

Since 2008, propranolol has become the medical therapy of choice for IH requiring treatment. The serendipitous discovery that propranolol reduced IH size and redness occurred in 2008, and due to its effectiveness and excellent safety profile, it is now the first-line IH treatment.[20] Previously, propranolol was used in the pediatric population for hypertension, supraventricular tachycardia, prolonged QT syndrome and thyrotoxicosis.[21] Following 2008 in the United States, the generic liquid preparation of propranolol was used as an off-label therapy for IH. In Europe, where liquid propranolol was unavailable, Hemangeol™ was created and since 2014, it has been FDA approved for pediatric IH therapy.

Pharmacology

Propranolol is a non-selective beta-adrenergic receptor antagonist. The liver metabolizes the medication and 25% of oral propranolol reaches systemic absorption. The duration of action is 6-12 hours depending on dose and the peak effect occurs 2 hours after administration.[9,21]

Propranolol is contraindicated for patients who have cardiogenic shock, 1st degree AV block, heart failure, bronchial asthma, hypersensitivity to propranolol, resting heart rate and/or blood pressure 2 standard deviations below normal, unexplained syncope, impaired renal or liver function, <1 week of age and in patients who have to endure long periods of fasting.[9]

Propranolol for PHACES syndrome

PHACES syndrome consists of posterior fossa malformations, hemangiomas, arterial anomalies, coarctation of aorta and cardiac defects, eye abnormalities and sternal defects.[22] Recognizing cerebrovascular abnormalities in these patients is important because of the possible increased risk of ischemic stroke.[22,23] It has been suggested that steroids and propranolol in these patients could increase the risk of stroke, as steroids can cause hypertension and propranolol can cause hypotension.[17] Patients with suspected PHACES syndrome need evaluation before propranolol initiation to help prevent these complications.

Mechanism of Action

The mechanism of action by which propranolol disassembles IH vasculature, reducing intralesional vessel density, is unknown; while there are many theories seeking to explain this, there is no supporting evidence to fully adopt any of these theories.[24] It is unclear if propranolol inhibits angiogenesis through the beta receptor blockade, as these receptors are on all IH cells and are present in other vascular anomalies that are non-responsive to propranolol. Other studies have explored the role of the beta receptors in endothelial cells. They found that if the gene encoding the adrenergic receptor is lost, angiogenesis is inhibited; however, how this relates to IH regression with propranolol therapy remains unclear.[25,26] As discussed previously, certain miRNAs have been shown to be uniquely present in IH as compared to other vascular anomalies and one study focused on propanolol's ability to downregulate the miRNA, miR-382, that is also present in IH.[27] Propranolol may increase in the pro-apoptotic protein Bax and the decrease in the anti-apoptotic proteins Bcl-2 and Caspase3 in IH tissue.[28] Further studies are necessary to understand propranolol's molecular mechanism that stops IH growth.

Monitoring of Efficacy

Propranolol is efficacious in 50-88% of cases.[3,29] Studies reporting efficacy rates have used various measures to define success, such as decrease in astigmatism for periorbital IH, time to ulceration resolution, complete resolution in IH, reduction in size by 50%, and improvement in color.[8,11,30-32] Periocular hemangiomas showed a reduction in size by 40-47% with the use of propranolol.[30,33] Nasal hemangiomas are disfiguring and surgical excision is challenging, but propranolol therapy decreased surgical intervention for nasal hemangiomas by 56%.[34] Similarly airway hemangiomas treated with propranolol have reduced surgical interventions.[15]

Ultrasound is a non-invasive way of monitoring response to treatment more objectively and for deeper lesions.[24] As discussed above, C19MC is a microRNA cluster found to be upregulated in IH tumor endothelial cells and present in IH patient plasma. Plasma levels decreased in IH that were responsive to propranolol, but not in those that did not respond to propranolol. This could be a future tool to diagnose and monitor treatment.[13]

It is prudent to briefly mention that congenital hemangiomas [non-involuting congenital hemangiomas (NICH), rapidly-involuting congenital hemangiomas (RICH)|] are different entities compared to IH due to their presence at birth. NICH's do not express the GLUT-1 protein, express beta-adrenergic receptors, and persist as a patient grows.[35,36] RICH's similarly do not express the GLUT-1 protein; however, typically regress by 14 months of age.[37,38] Due to the rarity of these lesions, the true response rates to propranolol is unknown, but have anecdotally been less than that for IH.

Propranolol Initiation

Since the introduction of propranolol for IH treatment, its initiation is not standardized.[39] Previously, most institutions had IH patients evaluated by cardiology preinitiation to rule out any cardiac abnormalities that were treatment contraindications. Now after experience with propranolol for IH therapy, there is question of the utility of routine cardiology evaluation in

patients without risk factors.[40] Most patients are being treated by a multidisciplinary vascular anomalies clinic and the first dose is administered in clinic.[39] If the patient's heart rate or blood pressure is below 2 standard deviations of normal, if they are <6 weeks corrected gestational age, or if they have airway involvement, inpatient monitoring is recommended.[21]

Though not standardized, the recommended starting dose is 0.66 mg/kg/dose every 8 hours to scale to a final dose of 2 mg/kg/day.[41] Patients are treated for variable amounts of time depending on how well the lesion responds; however treatment for 6 months has been shown to be more effective than a shorter course.[30]

At Seattle Children's Hospital (SCH), patients 6 weeks of gestationally corrected age or older may start propranolol as an outpatient. The patient and family attend a visit to go through a cardiology screening checklist and teaching sessions regarding propranolol administration. The checklist was created with cardiology assistance to identify patients who need cardiology clearance before starting the propranolol. If the patient has any of the following, they are referred to cardiology: persistent poor oral feeding; persistent poor weight gain; baseline/persistent dyspnea, diaphoresis, tachypnea, tachycardia; syncope; congenital heart disease; brain malformations; family history of congenital heart disease, arrhythmia, sudden death before age 50, or connective tissue disorder; vital signs outside of the approved parameters by age; irregular heart rate or rhythm; pathologic sounding heart murmur; increased work and rate of breathing; hepatomegaly; cool extremities; delayed capillary refill; or probable or definite PHACES syndrome. At the medication initiation visit, the family is taught how to administer the medication. The patient is started at a dose of 1-2 mg/kg/day divided into 3 doses. The blood pressure and heart rate are checked 1, 2 and 3 hours after administration. The family is given a stethoscope and taught how to listen and calculate the heart rate at home for the first two weeks after propranolol initiation. The side effects and symptoms to prompt medical attention are reviewed.

Side Effects

Side effects may include: hypotension, bradycardia and hypoglycemia. Patients are observed at SCH for 3 hours after the first dose of propranolol to monitor for hypotension and bradycardia. Rarely, the hypotension and bradycardia become clinically relevant; however, parents are advised to check the patient's heart rate twice daily, 1-2 hours after the propranolol dose, for 2 weeks after initiating propranolol or if there are acute illnesses that could worsen hypotension (e.g. diarrhea).[42] Hypoglycemia is thought to be due to the inhibition of catecholamine-induced glycogenolysis and gluconeogenesis that can occur with fasting. The incidence of hypoglycemia is low (0.3%).[43] To avoid hypoglycemia, at the clinic visit, the family is educated about holding propranolol should the patient be fasting related to illness or other reasons. They may resume propranolol when on a normal diet. Pedialyte® can be helpful in these situations. If a patient has known asthma or an overlying viral illness, families are educated on observing for wheezing or symptoms of bronchospasms. This is also an infrequently encountered side effect (0.4%).[43] Even rarer side effects include hyperkalemia potentially from tumor lysis, and dental caries. Minor,

more common side effects include acrocyanosis and gastrointestinal and sleep disturbances.[9,44]

Propranolol is the first-line therapy for IH needing treatment. Further research into IH etiology will clarify propranolol's mechanism of action to help predict IH responsiveness and determine which patients will benefit most from therapy.

Vascular Malformations

Congenital vascular malformations may be composed of abnormal vessels of lymphatic, venous, or arterial origin. In many cases, a mixture of vessel types is present. The genetic etiology of some malformations has been described and is resulting in new medical therapeutic options. In the following sections, novel medical therapy for lymphatic, venous and arteriovenous malformations will be discussed.

Lymphatic Malformation

Description of Disease and Current Treatment—Lymphatic malformations (LM) are congenital lesions that occur between 1-3 per 6000 births.[45,46] It is estimated that 75% occur in the head and neck.[47,48] Radiologically, LM can be broadly categorized as microcystic (cysts <2 cm) or macrocystic (cysts ≥2 cm).[49] deSerres proposed a clinical LM staging system based on malformation laterality and anatomic relationship to the hyoid bone, to help predict prognosis and surgical complications (Table 2).[50]

Until recently, LM-induced overgrowth, dysfunction and/or disfigurement have been treated with excision and/or sclerotherapy.[51] Clinical behavior of LM varies and a careful retrospective study has found that some stage 1 and stage 2 LM can spontaneously regress, whereas stage 3 and 4 LM can cause aerodigestive tract dysfunction and resist cure.[52] When comparing sclerotherapy to surgical excision in large series, it has been found that low stage 1-3 LM represented 85% of all head and neck lesions and that both treatment modalities appeared to be equivalent in efficacy and resource utilization.[46,47,51,53] Even with this type of invasive treatment, large, high stage LM are associated with often unexplained systemic symptoms and complications that can consist of coagulopathy, chronic pain, cellulitis, ulceration, and visceral/bone involvement, that are unchanged by standard invasive therapy.[54]

Etiology of LM—A better understanding of the etiology of LM could lead to new treatment options. Recently DNA sequencing studies in LM tissue has led to the discovery that de-novo post-zygotic somatic mutations are the cause of LM. New approaches to DNA sequencing has enabled detection of de-novo post-zygotic somatic mutations in LM tissue and cells, revealing the cause of LM. Somatic mutations differ from germline mutations, present in all cells, as somatic mutations are only in affected cells that are located in varied anatomic locations, often causing unique phenotypic mosaicism.[55] Gain of function somatic mutations in PIK3CA, a kinase in the PI3K/AKT pathway, are present in LM tissue. When activated, PIK3CA promotes cell proliferation, growth, angiogenesis and protein synthesis. This gene is in the PI3K/AKT pathway that when activated, increases cell proliferation, growth, angiogenesis and protein synthesis (Figure 1).[56] Overactivation of this molecular

pathway correlates with the tissue overgrowth and persistence seen in high stage LMs.[57,58] Understanding the role of this pathway in the development of LM has opened the possibility of molecular based therapy and personalized medicine for LM patients.

Current Medical Practice—Identification of a disordered genetic pathway in LM tissue has encouraged investigators to apply treatment of other conditions with PIK3CA mutations and tissue overgrowth (i.e. tumors) to LM. Rapamycin inhibits a component of the PI3K/AKT1 pathway called mTOR, or mammalian target of rapamycin (Figure 1). Rapamycin is a macrolide that was first discovered from soil on Easter Island.[59] It has shown to be efficacious in other disease processes related to mTOR activation or when immune suppression is desired with solid organ transplants or autoimmune lymphoproliferative syndrome.[60,61] Recently, a phase 2 trial showed that empiric use of rapamycin in patients with complicated lymphatic malformations was safe and led to a decreased incidence of cellulitis, hospitalized days and frequency of infections. Side effects included gastrointestinal disturbances, metabolic toxicity such as lipid abnormalities, and blood/bone marrow abnormalities.[54] Response to treatment included reduction in lesional pain and bleeding, though complete responses were not common.[62] Lesional pain and mucosal bleeding in treated LM was diminished. Reasons for the lack of complete lesion response are unclear and future investigations will be necessary to determine optimal LM patient selection for this therapy.

Since head and neck LM are associated with significant morbidity and mortality, such as oral bleeding and pain, empiric supportive medical therapy directed at these symptoms is necessary, particularly in high stage LM. Corticosteroids can help decrease the inflammation associated with LM.[63,64] These drugs are most frequently necessary in adolescent patients with intraoral suprahyoid LM. Frequent intraoral trauma to a large infiltrating tongue lesion can precipitate inflammation, swelling, bleeding and pain. Antibiotics, along with corticosteroids, are used to treat these episodes and prolonged courses of antibiotics have been recommended to help prevent chronic infections.[65] A subset of patients with large, high stage LM may have lymphocytopenia.[66] These patients may have persistent and recurrent infections that may respond to a rotating schedule of prophylactic antibiotics. Occasionally, young patients with LM can present with acute episodes of enlargement of their malformation from intralesional hemorrhage. This intralesional bleeding can cause LM inflammation and even post hemorrhage anemia leading to inpatient admissions.

Clinical and base science research is ongoing that will ultimately lead to more reliable, biologically-based medical LM therapy. As this develops, methods to aid in standardizing outcome measures will be important to identify.[67]

Venous Malformations

Description of Disease and Treatment—Venous malformations (VM) are anomalies that are common in the head and neck region (40%). They are present at birth and continue to increase in size with the growth of the child.[68] The incidence is 2-5 in 10,000 births and they arise due to a discontinuous smooth muscle layer of developing venous channels. These malformed, dysfunctional venous channels expand erratically and infiltrate normal

surrounding structures.[69] They typically present with a bluish hue in involved skin or mucosa and are differentiated from deep hemangiomas by the presence of intermittent pain and dependent swelling.

The venous channels can also develop thrombi or phleboliths due to the venous stasis, inducing persistent VM enlargement. Enlargement can also occur during times of puberty and pregnancy with increased symptoms at those times.[70] Patients at risk for localized intravascular coagulopathy (LIC) are patients who have: 1). a large volume malformation (>10 mL), 2). presence of a phlebolith, 3). multifocal disease, or 4). history of Klippel-Trenaunay syndrome. These patients should have their pro-thrombin time, activated partial thromboplastin time, fibrinogen levels, D-dimer, and complete blood count tested.[71]

VM tend to grow with time and do not regress on their own. Much like LM treatment, VM treatment has primarily been invasive with either sclerotherapy or surgery. Observation is preferred if the lesion is in a location that does not have any functional compromise or symptoms. Sclerotherapy can be offered to help reduce pain and some of lesional volume by creating endothelial damage and channel fibrosis in symptomatic patients.[72] Surgery is also an option for localized malformations.[73] Surgery and sclerotherapy for VM, however, are associated with reliably high recurrent rates. As such, at SCH, our preferred treatment is a combination glue embolization surgery (GES) with the interventional radiology department. Intralesional glue embolization is done prior to surgical resection allowing more complete VM removal with better tissue planes, less intraoperative bleeding, and better identification of nerves.[74]

Etiology of VM—Most VM are sporadic.[75] However, there are familial cases of VM that have been linked to germline mutations in the TIE2 tyrosine kinase receptor (Figure 1).[76] This mutation has also been found in 50% of VM.[77] Since the vast majority of VM are sporadic and not familial, more research is being done to identify possible somatic mutations associated with the TIE2 pathway in patients with sporadic VM.[78] This investigation has shown that up to 27% of VM have associated PIK3A somatic mutations.[79]

Current Medical Treatment—In patients with more extensive lesions that are less amenable to invasive procedures, medical therapy can play a role. Low-dose aspirin, non-steroidal anti-inflammatory medications, or anticoagulation with enoxaparin is used as a prophylactic method to prevent thrombosis within VM as a way to reduce pain, especially in patients at risk for LIC.[80] In patients with lesions on the extremities, compression garments can provide enough pressure to these valveless lesions to prevent dilation and the pain that accompanies growth of the VM.[81]

As discussed previously, the TIE2 receptor plays a role in the development of some VM. The downstream pathway of TIE2 leads to the mTOR which then signals downstream to increase cellular growth and proliferation, similar to LM (Figure 1).[79] Additionally, the discovery that some VM are caused by PIK3CA has allowed rapamycin, an mTOR inhibitor, to provide an alternative treatment for painful, swollen VM in a small patient series.[79]

Arteriovenous Malformations

Description of Disease and Treatment—Arterio-venous malformations (AVMs) are high-flow, congenital vascular anomalies that are due to localized shunts (i.e. nidus) between the arterial and venous systems. AVMs present as warm, palpable, pulsatile lesions that can hemorrhage if epithelial or mucosal coverings are disrupted.[82,83]

The high vascular flow and growth causes surrounding tissue destruction, pain, ulceration, bleeding and cardiac overload.[84]

Treatment of AVM centers on nidus removal or ablation. Surgical resection can be offered in conjunction with embolization; however, disfigurement and effect on function can occur due to the invasive nature of the lesion into the surrounding tissues and need for complete removal.[85] Embolization alone is associated with high AVM recurrence compared to surgery, making it a suboptimal treatment. Ethanol sclerotherapy has shown some success; however, there is a need for multiple treatments and risk of cranial neuropathy if the lesion is in close proximity to the skull base or other critical structures.[86]

Etiology of AVM—Sequencing DNA from head and neck AVM tissue has shown somatic mutations of KRAS that adversely impacts vascular assembly by increasing downstream ERK signaling.[87] Other variants were noted in NRAS, BRAF and MAP2K1 genes that similarly are associated with vascular assembly.[88] While this is very exciting, it is too early to tell whether this will result in a biologically based medical AVM treatment.

Current Medical Treatments—Surgery and embolization are imperfect methods of AVM treatment. There is a need for novel, more effective therapies. Molecular pathways recently identified in the development of these lesions could potentially be inhibited improving treatment. A proposed theory is that the endothelial dysfunction that causes AVMs is due to the increased activity of the mitogen-activated protein kinase kinase (MAP2K1), also known as MEK1 (Figure 1). MEK1 inhibitors are used in cancers and can have a potential application in AVM.[89]

Conclusion

Medical therapy for vascular anomalies has become more prominent as a treatment modality. As genetic and molecular testing becomes more sophisticated, precision medicine may direct medical and surgical therapy of these complex lesions. Medical and surgical therapy that can remove or destroy diseased cells may have advantages over other treatment modalities. Careful evaluation of all patients with vascular anomalies with a multidisciplinary team, including surgical specialists, geneticists, interventional radiologists, dermatologists, and hematologists/oncologists, is needed to help make the most efficient and effective treatment decisions.

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General Comments

1. Not all vascular lesions are infantile hemangiomas. Careful attention to the history and time course can help distinguish between vascular anomalies.
2. Patients who have lesions that require surgical or medical therapy that is beyond the comfort level of the pediatrician, lesions unresponsive to first-line therapy, or complicated vascular lesions (e.g. ulceration, chronic pain, airway or intracranial involvement, bleeding, coagulopathy, etc.) would benefit from a consultation to a vascular anomalies center. Vascular anomalies centers offer multidisciplinary care and up to date treatment methods.
3. Molecular genetics has furthered our understanding of the etiology of vascular anomalies and has aided in the introduction of novel medical therapies.

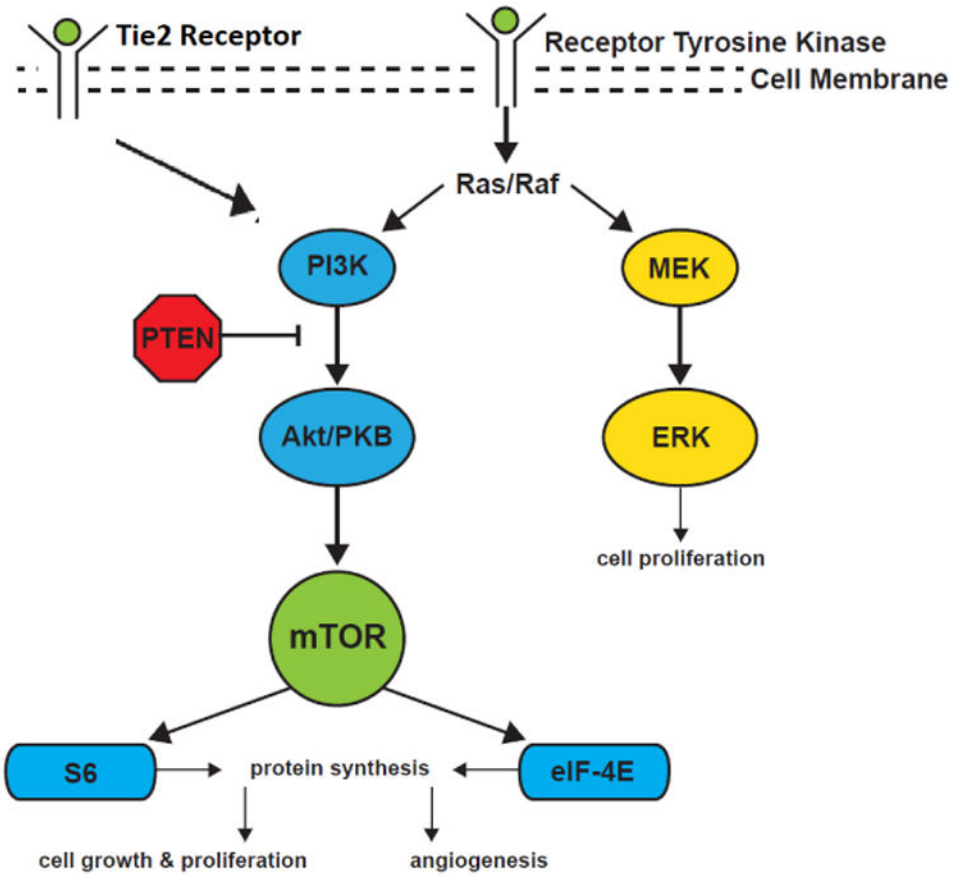

Figure 1.
PI3K/AKT pathway and MEK pathway leading to cell growth and proliferation.

Table 1
ISSVA 2014 Vascular Anomalies Classification Scheme and Associated Genetic Basis

Abbreviations: CM, capillary malformations; AVM, arteriovenous malformations; CNS, central nervous system; HHT, hereditary hemorrhagic telangiectasia; CMTC, cutis marmorata telangiectatica congenita; VM, venous malformation; CCM, cerebral cavernous malformations; JPHT, juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome; MCAP, macrocephaly-capillary malformation; MICCAP, microcephaly-capillary malformations; PIK3CA, phosphatyidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha

Capillary Malformations	
Cutaneous and/or mucosal CM (port wine stain)	GNAQ
CM with bone and/or soft tissue hyperplasia	-
CM with CNS and/or eye anomalies (Surge-Weber)	GNAQ
CM of CM-AVM	RASA1
Telangiectasia	-
HHT	-
HHT1	ENG
HHT2	ACVRL1
HHT3	-
Others	-
CMTC	-
Nevus simplex/salmon patch	-
LM	
Primary lymphedema	-
Nonne-Milroy syndrome	fLT4/VEGRFR3
Primary hereditary lymphedema	VEGFC
Primary hereditary lymphedema	GJC2/connexin 47
Lymphedema-distichiasis	FOXC2
Hypotrichosis-lymphedema-telangiectasia	SOX18
Primary lymphedema with myelodysplasia	GATA2
Primary generalized lymphatic anomaly	CCBE1
Microcephaly with/without chorioretinopathy	KIF11
Lymphedema or mental retardation syndrome	-
Lymphedema-choanal atresia	PTEN14
VMs	
Common VM	TIE2 somatic
VMCM	TIE2
Blue rubber bleb nevus (Bean) syndrome VM	-
Glomuvenous malformation (VM with glomus cells)	Glomulin
CCM	-
CCM1	KRIT1
CCM2	Malcavernin

Capillary Malformations	
CCM3	PDCD10
AVMs	
Sporadic in HHT	-
HHT1	ENG
HHT2	ACVRL1
JPHT	SMADA4
CM-AVM	RASA1
AVFs	
VMs associated with other anomalies	
Klippel-Trenaunay syndrome	-
Parkes Weber syndrome	RASA1
Servelle-Martorell syndrome	-
Sturge-Weber syndrome	GNAQ
Limb CM + congenital nonprogressive limb overgrowth	-
Maffucci syndrome	-
MCAP	PIK3CA
MICCAP	STAMBP
CLOVES syndrome	PIK3CA
Proteus syndrome	AKT1
Bannayan-Riley-Ruvalcaba syndrome	PTEN
Provisionally unclassified Vascular Anomalies	
Verrucous hemangioma	-
Multifocal lymphangioendotheliomatosis with thrombocytopenia/cutaneovisceral angiomatosis with thrombocytopenia	-
Kaposiform lymphangiomatosis	-
PTEN (type) hamartoma of soft tissue/angiomatosis of soft tissue	PTEN

Table 2

deSerres Classification Scheme for Lymphatic Malformations

Stage	Location
I	Unilateral infrahyoid
II	Unilateral suprahyoid
III	Unilateral suprahyoid and infrahyoid
IV	Bilateral suprahyoid
V	Bilateral suprahyoid and infrahyoid