Techniques in Vascular and Interventional Radiology

Practical Genetic and Biologic Therapeutic Considerations in Vascular Anomalies

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Vascular anomalies are classified as either tumors or malformations based on clinical findings rendered through radiologic evaluation, physical exam, and histologic interpretation. These findings comprise the phenotype of the disorder. Recently, advances in the molecular genetics of vascular anomalies have shed light on the genotype of these disorders. These phenotype/genotype characterizations will provide a more precise classification of vascular anomalies and identify potential therapeutic targets for expanded treatment options in the future. In this chapter, we will review the phenotype/genotype characterizations and the possible therapeutic pathways for targeted pharmacologic therapy.
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Introduction

Vascular anomalies are characterized as either tumors or malformations.[1] Tumors proliferate and grow while vascular malformations are congenital abnormalities of the vasculature and are characterized by the type of vessels that are abnormal such as venous, arteriovenous, capillary, lymphatic, or combined lesions. Vascular anomalies have been further characterized into syndromes described because of similar clinical characteristics such as Klippel-Trenaunay syndrome, extensive capillary-lymphatico-venous malformation with hypertrophy, PTEN hamartoma tumor syndrome, CLOVES (Congenital, Lipomatous, Overgrowth, Vascular Malformation, Epidermal Nevi and Spinal/Skeletal Anomalies) and Parkes Weber Syndrome-capillary malformation/arterial venous malformation with or without lymphatic overgrowth to name a few. For both tumors and malformations the diagnosis or phenotype is based on the physical exam and the radiologic and pathologic findings.[2,3,4] In the past most vascular anomalies were treated with surgical and or radiologic interventions. Medical management was not based on pathophysiology or molecular targets but on experience of use mostly in hemangiomas and other tumors. Thus there was limited evaluation of assessment of response and no prospective clinical trials.

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Genetic Basis of Vascular Anomalies

Though the majority of vascular anomalies form sporadically, the genetic basis of vascular anomalies was first identified in rare familial cases. These familiar forms account for (1%-20%) of vascular malformations and include capillary malformations, venous malformations, and cerebral cavernous malformations.[5,6] With this discovery, scientists hypothesized that the majority of vascular anomalies may be caused by somatic mutations which were proven with the development of next-generation sequencing. It is important for the clinician to understand the familial vs sporadic vascular anomalies as this information will affect the diagnosis, treatment plan, and the discussion of long term outcomes.

A germline mutation is a detectable variation within germ cells. These are the only mutations that can be passed on to offspring when either the mutated sperm or oocyte come together to form a zygote. A somatic mutation is caused by a random, acquired variation to the genetic sequence of a cell any time after fertilization. It is passed on to only the affected cell's progeny and not to the organism's offspring. A germline mutation can be found in the blood, buccal cells or the tissue vs a somatic mutation which for now can only be found in the lesional tissue. The multiple germline and somatic mutations found in vascular anomalies are noted in Tables 1 and 2.

Mutations are also characterized by the gene and signaling pathway involved as well as the cell(s) enriched for the mutation.[7] Recent discovery has revealed that vascular anomalies are known to be largely due to disrupted endothelial receptor intracellular signaling pathways involved in the PI3kinase(K)—AKT, MAPK, and SMAD signaling pathways (Fig. 1).[8-12]

Table 1 Familiar Vascular Anomalies are Commonly Autosomal Dominant and Result in Loss of Function of a Gene. The Disorder is Usually Caused by a "Second Hit" Phenomenon

Diagnosis (Phenotype)	Gene (Genotype)
Glomovenous malformation (GVM)	Glomulin
Mucocutaneous venous malformation (VMCM)	TEK/TIE2
Hereditary hemorrhagic telangiectasia (HHT):	
HHT 1	Endoglin (ENG)
HHT 2	ACVRL1
HHT – juvenile polyposis	SMAD4
CV-AVM 1	RASA1
CV-AVM 2	EPHB4
Cerebral cavernous malformations (CCM-multifocal)	KRIT1/CCM1 Malcavernin/CCM2 Programmed cell death 10 (PDCD10/CCM3)
PT hamartoma syndrome	PTEN
Primary lymphedema	VEGFR3/FLT-4, FOXC2, SOX18, CCBE1

Table 2 Vascular Anomalies are Caused Most Commonly by Somatic Mutations. Most Mutations are Activating With Variable Mutant Allele Frequency

Diagnosis (Phenotype)	Gene (Genotype)
Venous malformation (VM)	TEK/TIE2, PIK3CA
Multifocal venous malformation (MVM)	TEK/TIE2
Blue rubber bleb nevus syndrome (BRBN)	TEK/TIE2
Capillary malformation (CM)	GNAQ, GNA11
Verrucous venous malformation (VVM)	MAP3K3
PROS (CLOVES, FAVA, MCM, FIL, KTS)	PIK3CA
Lymphatic malformation (LM)	PIK3CA
Generalized lymphatic anomaly (GLA)	PIK3CA
Proteus syndrome/MCM	AKT
Arteriovenous malformation	KRAS, NRAS, BRAF, MAP2K1
Congenital hemangioma (RICH, NICH)	GNAQ, GNA11
Pyogenic granuloma	GNAQ, KRAS
Kaposiform hemangioendothelioma (KHE)/tufted angioma (TA)	GNA14
Kaposiform lymphangiomatosis	NRAS

Special Consideration for Vascular Anomalies vs Oncology Diagnoses

Most of the causative somatic mutations in vascular anomalies are also noted in cancer; therefore repurposing selective cancer therapies based on molecular analysis may enhance vascular anomaly treatment options.[13] However, the strategy must be different than cancer. For example, as vascular anomalists our goal is to treat a vascular anomalies as we support normal growth elsewhere thus our goal is to reduce or modify problematic vascular endothelium not eliminate. In the past when dosing a new agent for an oncologic diagnosis, the aim was to increase the dose to a maximum tolerated dose. In vascular anomalies, the need is for stability of the endothelium which will most likely require as much lower dose of medication. This has been supported recently in early phase I/II studies with new agents (Miransertib and Alpelisib).[14,15] The length of treatment needed for vascular anomalies is presumed to be life long and thus consideration of short- and long-term toxicity is imperative.

New Therapeutic Options

The PIK3CA pathway was hypothesized to be involved in lymphatic and other anomalies prior to the use of sirolimus in a complicated patient with Kaposiform Hemangioendothelioma and then was the basis for the Phase II study supported by the FDA.[16,17] This also led to the development of treatment strategies for other vascular anomalies with significant improvement in the quality of life of these patients.

There is now preclinical and clinical data supporting the essential regulatory function of the PI3 kinase/AKT/mTOR pathway in vascular growth and organization and evidence now that mTOR inhibitors such as sirolimus are effective in the treatment of a large percentage of vascular anomalies. Unfortunately a percentage of anomalies continue to have poor overall survival even with improved time to disease exacerbation with sirolimus such as Kaposiform lymphangiomatosis.[17,18] Other patients do not respond to sirolimus such as arteriovenous malformations. Therefore new treatment options are necessary.

A recent publication using the PIK3CA inhibitor BYL719 for PIK3CA-related overgrowth syndromes revealed promising results.[14] Nineteen patients were treated following a compassionate use protocol in France. Significant improvement in clinical symptoms and radiologic parameters were noted. This medication is only available for compassionate use but future studies in vascular anomalies are anticipated. Furthermore, there have been recent discovery of other somatic mutations identical to those found in cancer in the RAS-MAPK-ERK pathway.[19-21] These mutations include EPHB4, KRAS, HRAS, NRAS, BRAF, and MAP2K1. These discoveries are important as some of these somatic mutations are founds in the most high-risk vascular anomalies such as Kaposiform Lymphangiomatosis (NRAS) and extracranial arteriovenous malformations (MAP2K1). Protocols presently in use in pediatric oncology using MEK inhibitors may be effective for these patients. Studies are presently in development.

Conclusion

The molecular landscape of vascular anomalies is rapidly evolving. With the advancement of massively parallel sequencing, it is now possible to perform high-throughput screens on tissue samples. Furthermore, targeted panels for known mutations are now available at many centers. It is clear that when tissue is

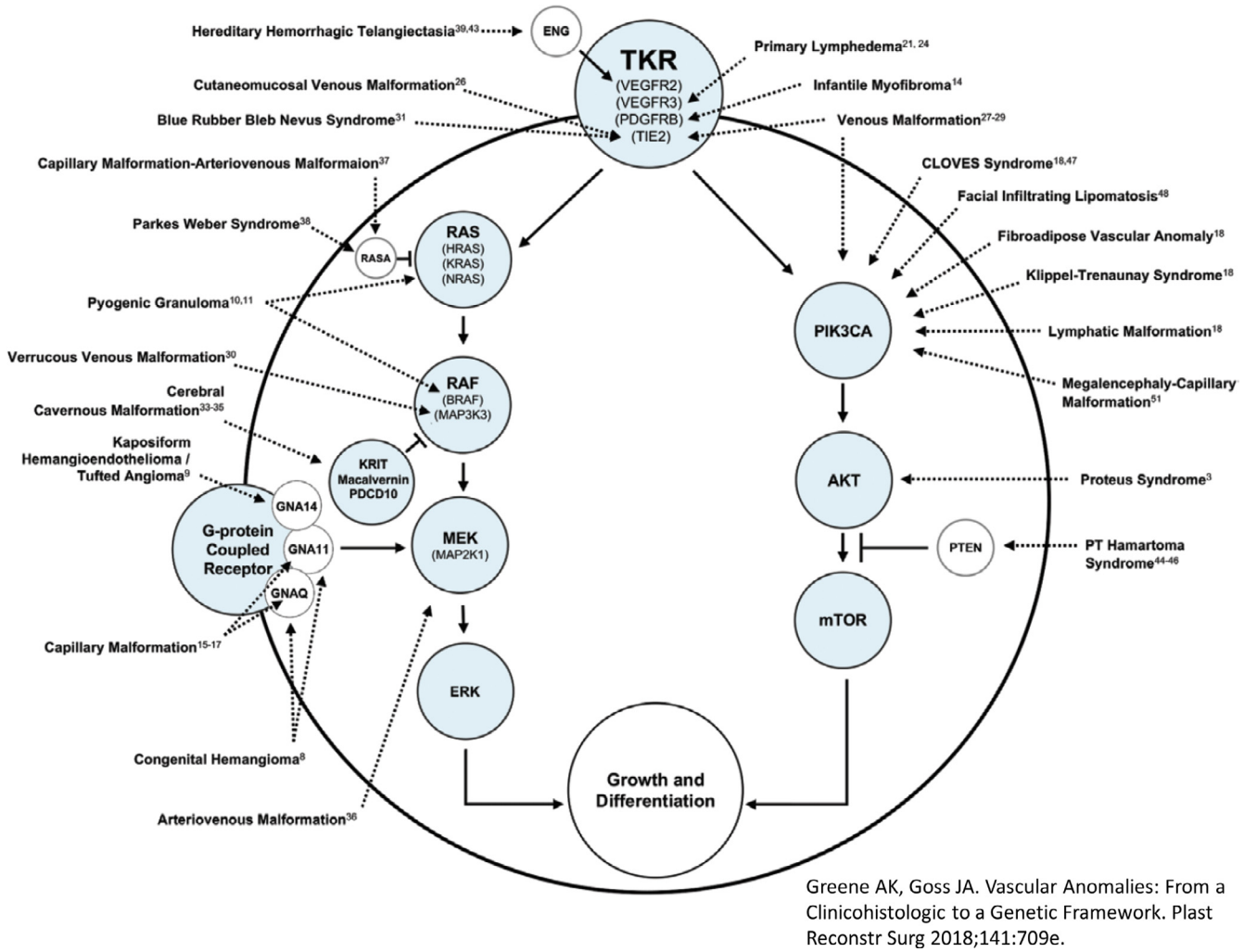

Figure 1. Vascular anomalies for the hematologist/oncologist

available genotyping a patient is essential. The genotype will be important as new therapeutic options become available through prospective clinical trials. In the future, other forms of drug delivery are also being investigated.

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