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Targeted treatment of vascular anomalies

Ashley T. Ng BS[a,*], Richard L. Tower[b], Beth A. Drolet[a]

[a] Department of Dermatology School of Medicine and Public Health, University of Wisconsin, Madison, Wisconsin
[b] Department of Pediatrics, Medical College of Wisconsin, Madison, Wisconsin

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ABSTRACT

Vascular anomalies comprise an array of congenital developmental disorders that can lead to significant disfigurement and physiologic disarray. The vast multitude of clinical phenotypes has inherently led to misdiagnosis and patients and families enduring long diagnostic odysseys of medical care. Although the observed variation in disease manifestations remains poorly understood, targeted next-generation sequencing has pivoted our understanding of the pathobiology of vascular anomalies and, for the first time, uncovered potential pharmacologic targets for these disorders. In this review article, we highlight current and developing targeted therapies for vascular anomalies, namely phosphoinositide 3-kinase and mitogen-activated protein kinase pathway inhibitors, and discuss the future directions of targeted therapies.

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* Corresponding Author:
E-mail address: ang@dermatology.wisc.edu (A.T. Ng).

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Table 1
Example of preliminary molecular classification of vascular anomalies

Gene	*PIK3CA, PIK3R1, PIK3R2, AKT-1, MTOR, TEK*	*KRAS, NRAS, RASA1, MAP2K1*	*GNAQ, GNA11*
Acronyms and clinical diagnoses	Klippel–Trenaunay syndrome, venous malformations, lymphatic malformations, megalencephaly-capillary malformation-polymicrogyria, congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal (CLOVES), PICK3CA-related overgrowth syndrome, diffuse capillary malformation and overgrowth, capillary malformation of the lower lip, lymphatic malformation of the face and neck, asymmetry and partial/generalized overgrowth, PIK3CA-related disorder, proteus syndrome, congenital lipomatosis	Arteriovenous malformation, Parkes–Weber, capillary malformation-arteriovenous malformation syndrome	Capillary malformations, port wine stain, Sturge–Weber, phakomatoses,
Targeted Therapy	Inhibitors of PI3K-AKT-mTOR Pathway (e.g. sirolimus, alpelisib)	Inhibitors of RAS-RAF-MEK-ERK pathway (e.g. trametinib)	Unknown

What is known about this subject in regard to women and their families?

- Vascular anomalies can be debilitating and are associated with severe tissue and bone overgrowth, structural birth defects, disorders of coagulation, and disfigurement.
- Patients and families with vascular anomalies are often misdiagnosed and endure long diagnostic odysseys with the medical care of their children.

What is new from this article as messages for women and their families?

- Targeted pharmacologic treatment of vascular anomalies has the potential to improve the lives of families affected by vascular anomalies.

Introduction

Vascular anomalies represent a heterogeneous group of rare, benign congenital developmental disorders that are often associated with significant morbidity and disfigurement. These disorders are remarkably variable, ranging from vascular lesions limited to the skin with mild soft tissue overgrowth to debilitating venous and lymphatic malformations with severe tissue and bone overgrowth (Klippel–Trenaunay syndrome [KTS]; congenital lipomatous overgrowth with vascular malformations, epidermal nevi, and scoliosis [CLOVES] syndrome) to structural birth defects that affect the eyes, brain (Sturge–Weber syndrome), and many other organ systems. Misdiagnosis is common due to the diversity in clinical presentation and confusing nomenclature.

No drugs have been approved by the U.S. Food and Drug Administration for treatment, and standardized treatment protocols have not been developed. The use of targeted next-generation sequencing (NGS) has demonstrated that many vascular anomalies are caused by mosaic mutations in highly conserved genes that control cell proliferation and survival (Cottrell et al., 2021; Keppler-Noreuil et al., 2014; Lindhurst et al., 2011; Madsen et al., 2018; Mirzaa et al., 2013; Siegel et al., 2018). This has transformed our fundamental understanding of the pathobiology of vascular anomalies and, for the first time, revealed potential pharmacologic targets for these disorders.

Rapid expansion in gene discovery has outpaced basic understanding of the natural history of vascular anomalies and exposed a gap in knowledge regarding the trajectory of disease progression and a lack of standardized outcome measures critical to the design of interventional trials. The goal of this review is to provide an overview of current and developing targeted therapies for vascular anomalies.

Advances in understanding of pathogenesis of vascular anomalies

Vascular malformations are currently subclassified as capillary, lymphatic, arterial, venous, and combined malformations. However, due to their formation during early embryogenesis, these lesions are frequently composed of primitive vessels with an admixture of several vessel types and may be associated with additional developmental defects. KTS is one of the most well-known phenotypes, with patients demonstrating complex malformations of veins, capillaries, and lymphatic vessels with soft tissue and bone overgrowth. The protean clinical phenotype and use of various naming schema to describe the vascular anomaly phenotypes has caused confusion in diagnosis, misperception regarding prognosis, and hindered progress in therapeutic intervention.

For example, capillary malformation, port-wine stain, reticulated capillary malformation, or nevus flammeus may all be used to describe the same low-flow vascular malformation. In addition, the term "port-wine" is often used to describe the deep-red vascular stains associated with postzygotic *PIK3CA* mutations. This can be especially problematic for patients who encounter this confusing terminology describing the same diagnosis. Some helpful acronyms have been used to contextualize complex syndromes, such as CLOVES syndrome. Less clinically descriptive eponyms, including KTS, do not capture the typical findings of port-wine stain, varicose veins, and bony/soft-tissue overgrowth and may be easily confused with other eponyms, such as Parkes–Weber syndrome, which shares several overlapping features.

NGS is rapidly enabling the discovery of pathogenic mutations within affected tissue and absent in genomic DNA, establishing somatic mosaicism as a cause of many vascular anomalies. This multifaceted genetic pathogenesis provides an explanation for variation and complexity of the phenotypic presentations. In 2011, Lindhurst et al. demonstrated mosaicism in affected tissue from patients with Proteus syndrome. This seminal discovery has subsequently led to the identification of mosaic mutations in several other vascular anomalies and related syndromes.

Most of these mosaic mutations occur in highly conserved genes that encode for intracellular proteins that tightly regulate the cell cycle (Table 1). Collectively, these genes control cell size, proliferation, migration, and apoptosis. Originally implicated in cancer, we now recognize that these genes are also critical regulators of fetal vascular development to such a degree that when mutations occur, even when mosaic and at very low allele frequency, they cause significant malformations and overgrowth in embryonic vasculature. This extraordinary set of discoveries has transformed

our fundamental understanding of the pathobiology of vascular anomalies and revealed novel potential pharmacologic targets for treatment of these congenital, but progressive, lesions.

Current barriers to clinical trials

The mosaic etiology and resultant clinical heterogeneity and segmental distribution of vascular anomalies has complicated disease nomenclature and classification. The segmental distribution of disease results in the development of vascular malformations in many organs, either in isolation or in association with multiorgan disease. Consequently, many distinct subspecialties have cared for patients and created specialty-specific acronyms and classification schema. Gene discovery has demonstrated that many of these acronyms and syndromes represent identical molecular diagnoses (Table 1). For example, patients with megalencephaly-capillary malformation-polymicrogyria syndrome have mosaic mutations in *PIK3CA*, as do many patients classified as having KTS. The affected tissue may be different, but both syndromes will likely benefit from the same pharmacologic inhibition.

In recent years, tertiary care institutions have begun to construct multidisciplinary teams dedicated to the care of these patients. Recent advances realized by NGS have not only transformed therapeutic options but have also provided a unified molecular explanation for historical confusion around diagnosis and classification. We believe specialists should move to develop a shared molecular-based language to bridge specialty-specific diagnoses and acronyms. A classification system that better reflects the recent advances in the understanding of the underlying molecular changes and their roles in pathogenesis will guide therapeutics and the design of clinical trials.

There is still an absence of observational natural history studies and clinically meaningful outcome measures for therapeutic interventions for vascular anomalies. Significant strides are being made to develop outcome measures that capture patient values and address the heterogeneity of this patient population (Lokhorst et al., 2021). Because gene discovery is outpacing the understanding of the resultant downstream molecular effects and genotype–phenotype correlations, patients are receiving off-label drugs outside of clinical trials in hopes of relieving symptoms; however, validated outcome measures of therapeutic response are lacking. Natural history studies could provide longitudinal data on disease severity, incidence, and patterns of progression to be used in deciding inclusion criteria, what stage of disease to treat, trial duration, and frequency of data collection. Once clinically meaningful outcome measures have been validated, the shared molecular basis of cancer can be leveraged to implement novel uses for existing cancer drugs for vascular anomalies.

Opportunity to repurpose cancer drugs

By identifying the shared molecular basis of vascular anomalies and solid tumors, we have set the stage for repurposing targeted therapies originally developed for cancer. This will shift treatment paradigms from surgical debulking/ablation of malformed tissue toward personalized and targeted pharmacologic intervention. There are no FDA-approved pharmacologic therapies to treat vascular anomalies; however, recent studies have demonstrated that sirolimus, an inhibitor of mammalian target of rapamycin (mTOR), is effective for venous and lymphatic malformations. Researchers and clinicians across disciplines are working to repurpose small molecules in the development for cancer that selectively inhibit activated pathways.

PI3K/Akt/mTOR pathway

As research into the causes of vascular anomalies has intensified, the phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR signaling pathway has been identified as an important regulator of normal tissue and vasculature development. Somatic mutations in *PIK3CA, PIK3R1, PIK3R2, AKT1, AKT3,* and *TEK* lead to hyperactivation of the PI3K signaling pathway, which results in abnormal tissue growth, angiogenesis, and lymphangiogenesis. Activating mutations in this pathway have been identified in vascular tumors, vascular malformations, and many disorders associated with tissue overgrowth (Cottrell et al., 2021; Davies et al., 2021; Rivière et al., 2012).

The term *PIK3CA-related overgrowth spectrum* has been proposed to encompass several vascular-related phenotypes, including CLOVES syndrome, megalencephaly–capillary malformation-polymicrogyria syndrome, congenital lipomatous overgrowth, and KTS, that result from these activating mutations. Therefore, the PI3K/Akt/mTOR pathway was identified as a possible target for intervention in patients with vascular tumors and malformations.

The medication specifically targeted to inhibit this pathway with the longest track record of success is sirolimus, an mTOR inhibitor. The efficacy of sirolimus in treating patients with vascular tumors and malformations was demonstrated in a small case series (Hammill et al., 2011). This proof of principle led to a phase 2 clinical trial that showed that sirolimus was both effective and well tolerated in the treatment of these disorders (Adams et al., 2016). Other studies have mirrored these findings, confirming safety and a high rate of symptomatic improvement; however, significant improvement in objective outcomes measures has been difficult to demonstrate and rare, severe adverse effects of sirolimus therapy have been reported, including nephrotoxicity, anemia, and thromboembolic disease (Nguyen et al., 2019; Parker et al., 2019; Rössler et al., 2021; Sandbank et al., 2019). Both clinical and laboratory monitoring is required for patients on this medication. Sirolimus is now used to treat a wide variety of disorders, including kaposiform hemangioendothelioma (with or without Kasabach–Merritt syndrome), venous malformations, lymphatic malformations, generalized lymphatic anomalies, Gorham–Stout disease, and blue rubber bleb nevus syndrome (Rössler et al., 2021).

The PI3K signaling pathway has been a major cancer target, with several candidate inhibitors investigated in oncology trials (Garneau et al., 2021; López Gutiérrez et al., 2019). Recent publications have described the repurposing of these cancer drugs that directly target the PI3K complex. Venot and Canaud (2021) reported a significant reduction in vascular malformation volume and soft-tissue overgrowth in patients treated with the selective PI3K alpha-subunit inhibitor alpelisib under open-label, compassionate use. There is an ongoing industry-sponsored phase 2 trial on alpelisib for patients with vascular anomalies harboring pathogenic mutations in PIK3CA.

A recently published open-label, phase 1/2 trial using taselisib for the treatment of CLOVES syndrome and KTS failed to demonstrate significance in objective outcome measures and was stopped due to serious adverse events (Luu et al., 2021). Miransertib, an inhibitor of AKT, showed minimal to no regression of target lesions in an open-label phase 1/2 study treating patients with mosaic *AKT* or *PIK3CA* mutations (U.S. National Library of Medicine, 2021, ARQ 092 (Miransertib) in Proteus Syndrome. https://clinicaltrials.gov/ct2/show/NCT03094832 (accessed 20 September 2021). Patient-reported pain assessments improved in pediatric patients (Keppler-Noreuil et al., 2019). Further exploration is necessary to weigh the risks and benefits of these pharmacologic therapies in patients with vascular anomalies.

KRAS/RASA1-MEK inhibitors

KRAS is an effector molecule in the mitogen-activated protein kinase (MAPK) pathway that mediates activation of several downstream pathways implicated in the pathogenesis of certain cancers and other cellular proliferative disorders, including arteriovenous malformations (AVMs). Somatic activating *KRAS* and *MAP2K1* mutations have been recently uncovered in patients with sporadic intracranial and extracranial AVMs (Couto et al., 2017; Nikolaev et al., 2018). These findings were accompanied by inherent dysregulation of the RAS/MAPK pathway. Therefore, medications that inhibit this pathway are of interest in the treatment of AVMs.

Inhibitors of the KRAS signaling pathway are used as antineoplastic agents. *MAP2K1* encodes for MEK, a downstream protein kinase that phosphorylates MAPK and a promising target in the treatment of AVMs. In vitro, MEK inhibitors can reverse endothelial cell phenotypes in the setting of KRAS activation, such as increased expression of angiogenic genes and altered function of adherens junctions (Nikolaev et al., 2018). In two children treated off-label with oral trametinib, a MEK inhibitor, decreased AVM blood flow and vessel caliber were observed 6 months after treatment (Edwards et al., 2020; Lekwuttikarn et al., 2019). RASA1 is another molecular modulator of the RAS/MAPK pathway that may be targetable by MEK inhibitors (Hayashi et al., 2018). Overall, MEK inhibitors are a promising therapy for sporadic extracranial AVMs harboring mutations of the RAS/MAPK pathway, but long-term safety remains a notable concern as we cumulate additional longitudinal information.

Future directions

The elucidation of the upregulated signaling pathways in vascular anomalies and the introduction of targeted therapies has had a profound impact on the treatment of patients with these disorders. As the role of medical therapy continues to expand, there are plenty of gaps that need to be addressed. Management of patients with vascular anomalies requires a multidisciplinary team approach to best address multiorgan morbidities. More education should be accessible to both primary and specialty care providers because diagnosis and referral to multidisciplinary care is often delayed. Genetic testing for targetable mutations is available, but negotiating insurance coverage is a significant hurdle for both patients and providers.

These diseases are rare; thus, there is a need for rationally designed, cooperative group trials to rigorously test the rapidly growing number of targeted medications, including combination therapies; retrospective studies cannot provide the necessary scope of information. Because these agents will be used in children, pediatric dosing and long-term safety profiles are crucial. Better understanding of these new therapies will shift treatment paradigms from invasive surgical and interventional therapies to targeted pharmacologic intervention. Demonstrated excellence in interdisciplinary science specific to vascular anomalies will improve treatment, relieve suffering, and improve the quality of life of patients and their families.

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