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Review Article

Congenital Vascular Lesions, Could *MAPK* and PI3K Inhibitors Pave the Way to New Therapies?

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Abstract

Purpose of Review: Superficial vascular anomalies are a heterogeneous group of malformative and tumoral lesions, developed from various types of abnormal lymphatic and /or blood vessels. They are mostly benign but their clinical evolution can lead to dramatic cosmetic concern, functional impairment and even life-threatening conditions. Until recently, treatments relied on invasive procedures such as embo /sclerotherapy and/ or surgery. Recent molecular findings pave the way of new medical therapies.

Recent Findings: Two main signaling pathways PI3K-*AKT*-mTOR and RAS-*MAPK*-ERK are now identified to encounter for the causative pathogenic genetic variants of most vascular anomalies. Involved genes are also responsible for several common neoplasms for which targeted therapies are already available or under development. Repurposing treatment strategy is considered for vascular anomalies treatment with promising results.

Summary: The mTOR inhibitor Sirolimus is the most used targeted therapy so far, but new molecules are tested currently.

Key Points

- The understanding of pathophysiological mechanisms in superficial vascular anomalies has dramatically improved, leading to the identification of causative genes of most vascular conditions.
- The causative genes of vascular anomalies are also implicated in several common neoplasms for which targeted therapy are already available or are in developing process, then repurposing strategy is considered.
- While Sirolimus is the most used targeted therapy with important data supporting its efficacy, other treatments such as alpelisib, and trametinib are tested currently.

Introduction

Congenital vascular malformations regroup a large field of various benign lesions made of different types of vessels. A majority of them are sporadic inborn vasculogenesis errors.

The first classification initiated in 1982 by Mulliken and Glowacki [1] was based on clinical features, natural history, cellular turnover and histology. The vascular tumors characterized by cell hyperplasia were first separated from vascular malformations made of various types of dysplastic vessels. Vascular malformations were subclassified according to flow characteristics (slow or high flow) studied on imaging and subsequently to immunostaining characteristics (GLUT 1 immunostaining and lymphatic markers) [1].

During the last 10 years, genetic research has dramatically improved, leading to the identification of the pathogenic variants of most of the known vascular anomalies, implemented in the last update of the classification in 2018 [2,3]. Those recent insights on the genetic basis of vascular anomalies pave the way to potential new therapies.

Vascular Malformations

Clinical presentations of vascular malformations are variable and represent a large spectrum ranging from asymptomatic birthmarks « angiomas » to large life-threatening conditions. They are present at birth and grow slowly with the patient.

Slow-flow vascular malformations encounter for capillary malformations, lymphatic malformations and venous malformations. High-flow vascular malformations consist of arteriovenous malformations and arteriovenous fistula.

Capillary malformations also named port-wine-stains consist of pink or red macules, present at birth and persistent through life, responsible for cosmetic concern.

Lymphatic malformations consist of dilated lymphatic channels or cysts. They can be microcystic, macrocystic, or mixed and are mostly located in soft tissue. Main symptoms are painful inflammatory flares with bleeding and lymph leakage, as well as cosmetic concern. In rarer multifocal presentations (generalized lymphatic anomaly and Gorham disease) organ involvement, mostly bone, but also spleen and lung may be observed, with more severe symptoms such as bone fractures, pleural effusion.

Venous malformations are usually unifocal soft compressible subcutaneous masses with bluish skin discoloration. Recurrent thrombophlebitis occurring within the enlarged vessels is a typical

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feature, leading to chronic, sometimes severe pain responsible for functional impairment. They occur mostly sporadically, but few familial forms exist.

Arteriovenous Malformations (AVMs) are much rarer vascular anomalies, composed of malformed arteries, veins, and capillaries. They are present as warm painful pulsating lesions. Complications consist of ulceration, which can lead to severe bleeding and cardiac overload which may be complicated by heart failure, due to arteriovenous shunting.

A range of vascular malformations syndromes composed by a combination of slow and/or high flow lesions and other tissue anomalies, in particular overgrowth, can also be observed.

Genetics

Recent biological and molecular findings with Next Generation Sequencing techniques (NGS) have considerably improved during the last decade in exploring vascular malformations. Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS) have been performed in the blood and on affected tissue of patients [4,5]. In most sporadic presentations, a pathogenic variant was identified within the tissue, but not in the blood; the occurrence of such a post-zygotic variant is the pathogenic basis of mosaic disorders, that include most of vascular anomalies. Two pathways are now well identified in the pathogenesis of vascular anomalies. The PI3K/*AKT*/mTOR pathway which is implicated in many cellular processes, such as cell-cycle regulation, proliferation, protein synthesis, and cell survival, and the RAS/*MAPK*/ERK signaling pathway, involved in cell-cycle regulation, cell proliferation, and migration [6]. A high-throughput sequencing study carried out using 319 tissue samples from patients with vascular malformations revealed a somatic variant in one of the players in these pathways in approximately 50% of patients [7].

TEK variants encoding for the *TIE2* protein located right upstream the *PIK3CA* PI3K/*AKT*/mTOR pathway were first identified in familial and then sporadic forms of VM.

In familial forms of VM a germinal variant in *TEK* is identified in most of cases but a second somatic "hit" is necessary for the development of lesions. This paradominant model of inheritance was also described for other rare familial forms of vascular malformations like Glomuvenous malformations or syndromic forms like CM-AVM1 or recently in vascular malformations of hereditary hemorrhagic telangiectasia patients [8-10].

Since then, many pathogenic somatic variants were identified in *PIK3CA* in several types of vascular malformations including simple slow-flow Vascular Malformations (VM, LM) and rare subtypes such as Fibroadipose Vascular Anomaly (FAVA), as well as combined vascular anomalies such as Congenital Lipomatous Overgrowth Vascular Epidermal and Squeletal anomaly (CLOVES), Klippel-Trenaunay Syndrome (KTS) or Megalencephaly-Capillary Malformation (MCAP) belonging to the spectrum of *PIK3CA*-related overgrowth syndrome or in generalized lymphatic anomalies. Variants in other genes of the pathway were also identified like in *PTEN* hamartoma tumor syndrome and Proteus Syndrome respectively associated to germinal *PTEN* variants and somatic *AKT1* variants. Two others inherited diseases are more indirectly linked to *PIK3CA*/*AKT*/mTOR pathway namely Hereditary hemorrhagic telangiectasia associated to loss-of function mutations in *ACVRL1* and *ENG* and glomuvenous malformations associated to GLMN variants. Indeed, it was shown that *ACVRL1* deficiency leads to increased PI3K pathway activation and that pharmacological PI3K inhibition prevents AVM formation in a mouse model deficient for *ACVRL1* [11].

Somatic pathogenic variants in genes involved in the RAS/*MAPK*/ERK pathway are mainly responsible for arteriovenous malformations. *MAP2K1* variants were identified in extracranial AVM and *KRAS*/*BRAF* variants were identified in cerebral AVM. The guanine nucleotide-binding protein subunit alpha q (Gαq) is an upstream element of the *MAPK* pathway composed by several subunits encoded by *GNAQ*, *GNA11*, and *GNA14* genes. Somatic gain of function mutations in *GNAQ* were identified in isolated CMs and Sturge-Weber syndrome and *GNA11* variants were identified in diffuse CM with overgrowth [12,13]. Interestingly, *GNA11* variants were described in congenital hemangioma and *GNA14* variants in Kaposiform Hemangioendothelioma (KHE) both high-flow vascular anomalies classified as vascular tumors. Various lymphatic anomalies were also associated to somatic variants leading to the activation of the *MAPK* pathway since NRAS variants were identified in kaposiform lymphangiomatosis and generalized lymphatic anomalies whereas ARAF variants were identified in patients presenting central conducting lymphatic anomalies [14]. It is of note that a germline EPHB4 mutation was also identified in one CCLA family [15].

Currently Genes related to *PIK3CA*/*AKT*/mTOR or RAS/*MAPK*/ERK pathways for which mutations have been described in vascular malformations are summarized in Table 1. Most of identified variants activate PI3K or *MAPK* pathways by sitting on very specific domains of growth factors, or by causing loss of function on growth inhibitor proteins. The discovery of these genetic abnormalities leads to consider the use of therapeutic molecules targeting these signaling pathways according to their molecular profile.

Targeted Therapies

Sirolimus

Sirolimus also named rapamycine is an inhibitor of mammalian Target of Rapamycin (mTOR), a serine/threonine kinase regulated by Phosphoinositide-3-Kinase (PI3K) and *AKT*. Once activated, the PI3K-*AKT*-mTOR pathway stimulates protein synthesis, cell proliferation and angiogenesis. Sirolimus was approved 20 years ago as an immunosuppressive therapy to prevent allograft reject in solid organs transplantation. It is also used for the treatment of tumoral manifestations of Tuberous sclerosis. Considering its antiangiogenic properties, sirolimus was given in several patients suffering from severe vascular anomalies, even before the identification of their causative pathogenic variant, with promising effects [16]. The identification of somatic variants belonging to the PIK3-*AKT*-mTOR pathway in several vascular malformations was a further clue to test the molecule. Since then, numerous reports and studies supported sirolimus efficacy mainly in slow-flow vascular malformations and in Kasabach-Merritt phenomenon associated to KHE [17,18] Sirolimus decreases the intensity and frequency of inflammatory flares in lymphatic malformations, as well as oozing from superficial LM [18,19]. Improvement of thrombo-inflammatory painful manifestations along with partial improvement of coagulopathy is observed in venous malformations [20]. Bleeding is also dramatically

Table 1: Genes related to *PIK3CA*/*AKT*/mTOR or RAS/MAPK/ERK pathways for which mutations have been described in vascular malformations.

Pathway	Disease	Gene	Mutation type
Slow-flow vascular malformations			
PI3K/AKT/mTOR	Multiple cutaneous and mucosal venous	*TEK*	G/G+S/S
	Sporadic Venous malformations	*TEK, PIK3CA*	S
	Blue rubber bleb naevus syndrome	*TEK*	S
	Lymphatic malformations	*PIK3CA*	S
	Fibro adipose vascular anomalies	*PIK3CA*	S
	Glomuvenous malformations	*GLMN*	G/G+S
RAS/MAPK/ERK	Verrucous Venous malformation	*MAP3K3*	S
	Isolated capillary malformations	*GNAQ*	S
High-flow vascular malformations			
RAS/MAPK/ERK	Extracranial Arteriovenous malformations	*MAP2K1*	S
	Cerebral arteriovenous malformations	*KRAS, BRAF*	S
PI3K/AKT/mTOR	Hereditary hemorrhagic telangiectasia	*ACVRL1, ENG*	G/G+S
Complex-combined vascular malformations			
PI3K/AKT/mTOR	Proteus Syndrome	*AKT1*	S
	PTEN hamartoma tumor syndrome	*PTEN*	G/G+S
	PIK3CA related overgrowth syndrome	*PIK3CA*	S
	Generalized lymphatic anomalies	*PIK3CA*	S
RAS/MAPK/ERK		*NRAS*	S
	Kaposiform lymphangiomatosis	*NRAS*	S
	Central conducting lymphatic anomalies	*EPHB4/*	G/S
	Sturge-Weber syndrome	*GNAQ*	S
	Diffuse capillary malformations with overgrowth	*GNA11*	S
	Capillary malformation-arteriovenous malformation type 1	*RASA1*	G/G+S
	Capillary malformation-arteriovenous malformation type 2	*EPHB4*	G

G: Germline mutation; G+S: Germline and Somatic second hit; S: Somatic mutation.

improved in angiokeratoma condition, and in mucosal involvement, especially gut involvement of venous malformation such as in Blue rubber bleb nevus [21]. However, in most cases, malformations size is not modified significantly [22]. Despite only few data, it seems that sirolimus may help in reducing the size in already inflammatory lesions, explaining the observation of dramatic volume reduction in lymphatic malformations treated with sirolimus right after sclerotherapy procedure [23]. Side effects mainly consist of mouse ulcers, rarely cytopenia, and dyslipidemia [18,20,22]. For superficial lesions topical sirolimus is considered, and seems to bring partial improvement [24-26].

Sirolimus demonstrated great efficacy in Kasabach-Merritt phenomenon related to KHE on both clinical and biological signs with almost no treatment failure to our knowledge [16,18]. Tumor dramatically shrinks along with coagulation blood tests normalization [27]. However, relapses are frequent after treatment discontinuation, then protracted treatment seems to be required [28]. The causative pathogenic variant identified in some cases is *GNA14*; *MAPK* pathway activation leads to the PI3K pathway activation, which may be the explanation for sirolimus effects in this condition.

AVM are now known to result from RAS/*MAPK*/ERK pathway variants, therefore sirolimus does not specifically target the involved signaling pathway [5]. However before molecular findings, sirolimus has been used sporadically in severe AVMs, because of bleeding, pain or high output cardiac failure. In our experience, efficacy appears to be inconstant. However partial improvement is sometimes observed, especially on bleeding but most of the time it is transient [29].

Other *PIK3CA-AKT*-mTOR Pathway Inhibitors

Several *PIK3CA* inhibitors are under development for *PIK3CA*-dependent tumors. Alpelisib Piqray®) was recently approved by the Food and Drug Administration for *PIK3CA*-mutated breast cancer treatment. In a mouse model of PROS/CLOVES, Alpelisib improved organ dysfunction. It has been tested in a clinical study treating 19 patients with PROS [30]. BYL719 treatment decreased vascular malformations size, reduced hemihypertrophy, attenuated scoliosis and improved general condition. Safety profile was satisfactory; rare mouse ulcerations were observed; hyperglycemia was monitored and corrected with nutritional modifications. In a further study including 40 patients, good safety profile was confirmed. The vascular component of the disease, especially lymphatic malformations showed dramatic size improvement.

Most Venous malformations result from *TEK*/*TIE2* mutations,

which is a tyrosine kinase receptor upstream *PIK3CA-AKT*-mTOR pathway [31]. Several Tyrosine kinase inhibitors are available. Li et al. [32] showed that a combination therapy with ponatinib and sirolimus promoted regression of venous malformations in a mouse model [32]. To our knowledge, no clinical trial is ongoing yet. Tyrosine kinase inhibitor may have severe side effects, therefore there may be some concern regarding benefit risk balance in children especially.

AKT can also be selectively targeted; ARQ 092, miransetib is currently under development for *AKT* related cancers. It showed moderate clinical improvement in a case report of Proteus syndrome [33].

Inhibitor of RAS-MAP Kinases Pathway

Arteriovenous malformations and other complex vascular anomalies, such as Kaposiform Lymphangiomatosis (KLA) and some Central Conducting Lymphatic Anomalies (CCLA) have been associated with somatic mutations occurring in the RAS/*MAPK* pathway. Theoretically MEK inhibitors such as trametinib may improve those conditions. A zebra fish model showed promising results [5]. In addition, a patient whose AVM harbored an activating in-frame deletion of *MAP2K1* responded well to trametinib treatment with a reduction in volume and symptoms, and with good tolerance [5]. However, in our unpublished experience, Trametinib did not show any improvement in a patient presenting with segmental AVM of the left superior limb associated with a superficial segmental verrucous epidermal nevus related to a *KRAS* causative mutation. Furthermore, the patient experienced severe side effects consisting of intense fatigue and severe erythematous and pustular skin rash, which required steroid therapy.

Conclusion

Congenital vascular malformations regroup a large field of various slow and high flow lesions and present a diagnostic and therapeutic challenge.

Recent advances molecular and genetic findings dramatically changed the treatment options in patients with large or complex vascular anomalies where neither surgery nor and endovascular treatment approach was efficient. They pave the way of new medical therapies using the two mains signaling pathways PI3K and *MAPK* improving considerably patients' symptoms, hope and quality of life.

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