Vascular Malformations: Current Progress Toward Drug Therapy

Arin K. Greene, MD and Christopher L. Sudduth, MD

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Vascular malformations are congenital disorders of vasculogenesis that affect approximately 0.5% of the population. Although benign, lesions cause significant morbidity, primarily because they enlarge over time. A common problem is psychosocial distress because most involve the integument resulting in a deformity. Other complications include: bleeding, pain, ulceration, loss of function, organ failure, and death.

Vascular malformations are differentiated from vascular tumors based on endothelial proliferation.[1] Vascular malformations classically have been considered quiescent lesions with minimal cellular turnover. Vascular tumors, in contrast, have significant endothelial division. Because of this discrepancy in cellular proliferation, vascular tumors, similar to other neoplasms, have been able to be treated with drugs. For example, infantile hemangioma responds to beta-blockers and corticosteroids, while kaposiform hemangioendothelioma is managed with sirolimus or vincristine.

Physicians who focus on patients with vascular malformations recognize that these lesions are not static. Vascular malformations *do* exhibit cellular activity and growth, although less than vascular tumors. Drug development for vascular malformations has been limited because:

(1) embryological structural problems are not believed to be amenable to pharmacotherapy,
(2) drugs used for vascular tumors in the past were not effective for malformations (eg, propranolol, prednisone), and
(3) the mechanisms by which vascular malformations enlarge are unknown.

Over the past several years tremendous growth in our understanding of the pathophysiology of vascular malformations has occurred. Our group has focused on understanding the biology of vascular anomalies to develop improved therapies. The first step in solving the mystery of vascular malformations is to determine their genetic basis. Technological advances in next-generation sequencing and bioinformatics have allowed the identification of low-level mutations in many somatic diseases, including vascular malformations (Supplementary Digital Content, Table 1, http://links.lww.com/SCS/C127).

Currently, the mutations responsible for most types of vascular malformations have been identified.[2] Variants typically affect tyrosine kinase signaling along either the RAS or PIK3CA pathways. Mutations usually are enriched in the endothelial cells. Although the mutations and cell-type driving the pathophysiology of the malformations are known, the mechanisms by which the mutation causes the malformation and results in its growth are being studied.

Now that the mutations for vascular malformations have been identified, investigators can test potential drug therapies on cell function in-vitro as well as attempt to develop in-vivo animal models. Although numerous types of vascular malformations exist, almost all of them fall under 4 major categories [capillary malformation, lymphatic malformation, venous malformation, arteriovenous malformation (Fig. 1)] that mirror the types of vasculature (capillaries, lymphatics, veins, arteries). Vascular malformations also contribute to overgrowth syndromes.

CAPILLARY MALFORMATION (CM)

Capillary malformation is the most common type of vascular malformation, affecting approximately 1/300 individuals. Lesions are present at birth as pink cutaneous stains. Capillary malformations darken, the skin thickens, tissues beneath the lesion become enlarged, and pyogenic granulomas can develop. First-line therapy is pulsed-dye laser to lighten the malformation; overgrowth of tissues is managed with resection. Unfortunately, CMs redarken and enlarge following treatment. Almost all CMs are sporadic and most are caused by mutations in *GNAQ*.[3,4] Diffuse lesions involving an extremity may result from *GNA11* or *PIK3CA* variants.[5,6] The cell-type enriched for the somatic mutations is the endothelial cell lining the blood vessels which is thus driving the pathophysiology of this lesion.[4] Although the mutations responsible for CMs are known, the biology by which the mutation causes the lesion and results in its growth remains unclear. Animal models of CM do not exist and targeted drug therapy has not been investigated experimentally or clinically.

From the Department of Plastic and Oral Surgery, Boston Children's Hospital, Harvard Medical School, Boston, MA.
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Address correspondence and reprint requests to Arin K. Greene, MD, MMSc, Department of Plastic and Oral Surgery, Boston Children's Hospital, 300 Longwood Ave., Boston, MA 02115;
E-mail: arin.greene@childrens.harvard.edu
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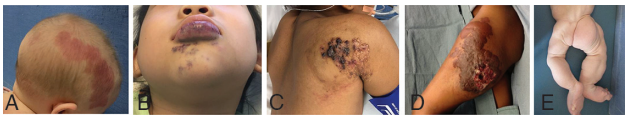

FIGURE 1. Major types of vascular malformations and an example of an overgrowth syndrome. (A) Capillary malformation. (B) Venous malformation. (C) Lymphatic malformation. (D) Arteriovenous malformation. (E) CLOVES syndrome.

LYMPHATIC MALFORMATION (LM)

Lymphatic malformations result from abnormal lymphatic development and cause bleeding, infection, pain, ulceration, and destruction of tissues. Treatment includes sclerotherapy, laser, or resection. Lymphatic malformations are caused by mutations in *PIK3CA*.[7] Primary lymphedema also is a type of LM and germline mutations in approximately 20 genes are known to cause this condition: *VEGFR3, VEGFC, CCBE1, FOXC2, GJC2, GJA1, PTPN14, SOX18, HGF, KIF11, PTPN11, SOS1, GATA2, IKBKG, RASA1, 15q locus, ITGA9, KRAS, RAF1, HRAS*.[8] Lymphatic malformation was the first vascular malformation to be successfully treated with targeted drug therapy using the mTOR inhibitor sirolimus (rapamycin) which blocks the *PIK3CA* signaling pathway.[9–11]

Lymphatic malformations currently are the most common type of vascular malformation treated with pharmacotherapy (Fig. 2A). Initially, only patients with very problematic lesions that had failed traditional treatments received the drug. Because sirolimus has a favorable toxicity profile, however, the indications for treating patients with this medicine have expanded. Sirolimus is now considered as first-line therapy in some patients and is used to reduce recurrence following sclerotherapy and resection. Recently, a genetically engineered mouse model of LM was developed and *PIK3CA* inhibitors showed efficacy.[12] Because *PIK3CA* mutations are the most prevalent variants in the field of vascular anomalies, pharmacotherapeutic development targeting this gene has received the most attention.

VENOUS MALFORMATION (VM)

Several germline and somatic mutations result in VMs and many exhibit a genotype-phenotype relationship. Mutations in the tyrosine kinase receptor *TIE2* cause both autosomal dominant cutaneomucosal VMs as well as most sporadic VMs.[13–15] Cerebral cavernous malformation (CCM) involves the brain and may be sporadic or autosomal dominant. Cerebral cavernous malformation can be associated with hyperkeratotic cutaneous lesions and are caused by mutations in *CCM1/KRIT1*, *CCM2/macalvernin*, or *CCM2/PDCD10*.[16] A glomulin mutation leads to autosomal dominant glomuvenous malformation. Glomuvenous malformations are small, multifocal, typically cause pain, and do not respond well to sclerotherapy.[17] A *MAP3K3* variant causes somatic verrucous venous malformations that is a hyperkeratotic lesion usually affecting an extremity.[18] Somatic VMs also result from *PIK3CA* mutations which typically are located subcutaneously.[19] Fibroadipose vascular anomaly, which was previously thought to be an intramuscular VM, results from *PIK3CA* variants.[7]

Venous malformations enlarge, especially during puberty, and are managed by sclerotherapy and resection. Like all vascular malformations, they can regrow following treatment. A favorable cell-based animal model exists for VM that has been used for drug testing.[20] Endothelial cells containing disease-causing mutations injected subcutaneously into immunodeficient mice create VMs that reasonably recapitulate the human phenotype. Sirolimus has shown efficacy against VMs in both animal models and humans.[20–22]

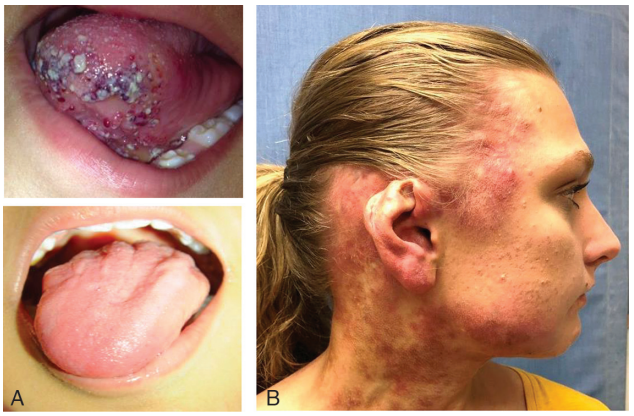

FIGURE 2. Current treatment of vascular malformations with pharmacotherapy. (A) Successful management of a tongue lymphatic malformation before (*above*) and after (*below*) oral sirolimus (photos courtesy of Cameron Trenor, MD). (B) Patient with an arteriovenous malformation treated with oral trametinib which improved her symptoms and slowed the progression of the lesion.

ARTERIOVENOUS MALFORMATION (AVM)

Arteriovenous malformation is an abnormal connection between arteries and veins without a normal capillary bed. Oxygen delivery to tissues is reduced and patients suffer from pain, bleeding, ulceration, deformity, and rarely congestive heart failure. Arteriovenous malformation is the most active "tumor-like" malformation and grows, especially during puberty. Arteriovenous malformation can be the most challenging type of vascular malformation to treat. Management includes embolization and resection. Unfortunately, AVMs have a high recurrence rate following these interventions.

Autosomal dominant hereditary AVMs can occur. Hereditary hemorrhagic telangiectasia causes epistaxis, telangiectasias, and visceral AVMs and results from mutations in *ENG*, *ACVRL1/ALK1*, *SMAD4*, or *GDF2*.[23] Capillary malformation-arteriovenous malformation and Parkes Weber syndrome are caused by germline variants in *RASA1* and *EPHB4*.[24–26] Germline *PTEN* mutations result in *PTEN* hamartoma-tumor syndrome; 50% of patients have AVMs that are typically multifocal, intramuscular, and have extra adipose tissue.[27]

Almost all AVMs are sporadic and most extracranial and intracranial lesions are caused by mutations in *MAP2K1* and *KRAS*, respectively.[28,29] Extracranial AVMs can result from *HRAS*, *BRAF*, and *KRAS* variants as well.[30–32] Mutations in *BRAF* also have been found to cause intracranial AVMs.[33] Although a genotype-phenotype association has not been present in intracranial AVMs, a relationship is emerging with extracranial AVMs. Lesions caused by *HRAS* variants have extra adipose tissue.[30] *KRAS* mutations are more likely to cause intramuscular fast-flow vascular anomalies and lesions that appear similar to congenital hemangiomas.[31,34] Arteriovenous malformation *MAP2K1* mutations are located in the endothelial cell and activate signaling causing tissue overgrowth by a cell nonautonomous mechanism.[28,35,36] The activating effects of the mutation in endothelial cells can be mitigated by treating the cells with a *MAP2K1* inhibitor.[35] Consequently, patients in our center and others are being treated with an FDA-approved *MAP2K1* inhibitor (trametinib) that was developed to treat melanoma and lung cancer (Fig. 2B). Results in our experience as well as published data show that for the first time a drug can prevent the growth of AVM as well as cause it to become smaller.[37,38]

VASCULAR MALFORMATION OVERGROWTH SYNDROMES

Capillary, venous, lymphatic, and arteriovenous malformations can be a major component of overgrowth syndromes. Proteus syndrome

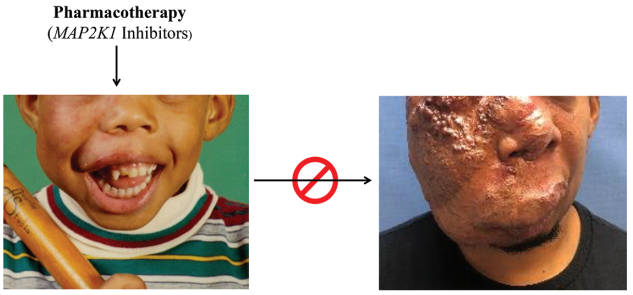

FIGURE 3. Future of drug treatment for vascular malformations. Our goal is to develop pharmacotherapy for patients that will prevent the enlargement of their lesions. In the future, this patient will receive medicine in childhood (*left*) that will stop his arteriovenous malformation from growing to cause significant morbidity in adulthood (*right*).

(progressive, asymmetrical overgrowth of the skeleton, cerebriform nevi of the hands or feet, epidermal nevi, vascular malformations, cerebral anomalies, skull hyperostosis, and megaspondylodysplasia) results from an *AKT1* mutation.[39] Maffucci syndrome (multiple enchondromas and soft-tissue VMs) is caused by variants in *IDH1/IDH2*.[40]

The most common overgrowth conditions result from *PIK3CA* mutations and are classified under the term PROS (*PIK3CA*-related overgrowth spectrum).[41,42] CLOVES syndrome (Congenital lipomatosis, overgrowth, vascular malformations, epidermal nevi, and skeletal anomalies), Klippel-Trenaunay syndrome (capillary-lymphatic-venous malformation of an extremity causing overgrowth), and facial infiltrating lipomatosis result from a *PIK3CA* mutation.[7,43,44] The mutation is present throughout all structures and is enriched in nonendothelial cells.[45] Megalencephaly-capillary malformation causes neurologic abnormalities and patients typically have a CM involving the upper lip, trunk, or extremity.[46] PROS conditions are being treated successfully in our center and others with sirolimus and *PIK3CA* inhibitors.[47–49]

CONCLUSIONS

It is a very exciting time in the field of vascular anomalies. Vascular malformations are at the crossroads of plastic surgery, basic research, innovation, and interdisciplinary collaboration. Molecular discoveries have been translated into clinical practice. We now use genetic testing to identify lesions with an unclear diagnosis, as well as to screen patients for potential drug treatment. We are at a point in time where we are transitioning from managing vascular malformations with resection, embolization, sclerotherapy, and laser to pharmacotherapy. Several FDA approved medications used off-label for vascular malformations have shown efficacy. In the future, drugs for vascular malformations will be a routine part of their management (Fig. 3). Medications will be used to prevent these lesions from enlarging, as well as reducing their risk of recurrence following "traditional" interventions.

REFERENCES

1. Wassef M, Blei F, Adams D, et al. Vascular anomalies classification: Recommendations from the international society for the study of vascular anomalies. *Pediatrics* 2015;136:e203–e214
2. Greene AK, Goss JA. Vascular anomalies: from a clinicohistologic to a genetic framework. *Plast Reconstr Surg* 2018;141:709e–717e
3. Shirley MD, Tang H, Gallione CJ, et al. Sturge–Weber syndrome and port-wine stains caused by somatic mutation in GNAQ. *N Engl J Med* 2013;368:1971–1979
4. Couto JA, Huang L, Vivero MP, et al. Endothelial cells from capillary malformations are enriched for somatic GNAQ mutations. *Plast Reconstr Surg* 2016;137:77e–82e
5. Couto JA, Ayturk UM, Konczyk DJ, et al. A somatic GNA11 mutation is associated with extremity capillary malformation and overgrowth. *Angiogenesis* 2017;20:303–306
6. Goss JA, Konczyk DJ, Smits P, et al. Diffuse capillary malformation with overgrowth contains somatic PIK3CA variants. *Clin Genet* 2020;97:736–740
7. Luks VL, Kamitaki N, Vivero MP, et al. Lymphatic and other vascular malformative/overgrowth disorders are caused by somatic mutations in PIK3CA. *J Pediatr* 2015;166:1048–1054
8. Brouillard P, Boon L, Vikkula M. Genetics of lymphatic anomalies. *J Clin Invest* 2014;124:898–904
9. Hammill AM, Wentzel M, Gupta A, et al. Sirolimus for the treatment of complicated vascular anomalies in children. *Pediatr Blood Cancer* 2011;57:1018–1024
10. Adams DM, Trenor CC, Hammill AM, et al. Efficacy and safety of sirolimus in the treatment of complicated vascular anomalies. *Pediatrics* 2016;137:e20153257
11. Rössler J, Geiger J, Földi E, et al. Sirolimus is highly effective for lymph leakage in microcystic lymphatic malformations with skin involvement. *Int J Dermatol* 2017;56:e72–e75
12. Martinez-Corral I, Zhang Y, Petkova M, et al. Blockade of VEGF-C signaling inhibits lymphatic malformations driven by oncogenic PIK3CA mutation. *Nat Commun* 2020;11:2869
13. Vikkula M, Boon LM, Carraway KL, et al. Vascular dysmorphogenesis caused by an activating mutation in the receptor tyrosine kinase TIE2. *Cell* 1996;87:1181–1190
14. Limaye N, Wouters V, Uebelhoer M, et al. Somatic mutations in angiopoietin receptor gene TEK cause solitary and multiple sporadic venous malformations. *Nat Genet* 2009;41:118–124
15. Soblet J, Limaye N, Uebelhoer M, et al. Variable somatic TIE2 mutations in half of sporadic venous malformations. *Mol Syndromol* 2013;4:179–183
16. Laberge-le Couteulx S, Jung HH, Labauge P, et al. Truncating mutations in CCM1, encoding KRIT1, cause hereditary cavernous angiomas. *Nat Genet* 1999;23:189–193
17. Brouillard P, Boon LM, Mulliken JB, et al. Mutations in a novel factor, glomulin, are responsible for glomuvenous malformations ("glomangiomas"). *Am J Hum Genet* 2002;70:866–874
18. Couto JA, Vivero MP, Kozakewich HPW, et al. A somatic MAP3K3 mutation is associated with verrucous venous malformation. *Am J Hum Genet* 2015;96:480–486
19. Limaye N, Kangas J, Mendola A, et al. Somatic activating PIK3CA mutations cause venous malformation. *Am J Hum Genet* 2015;97:914–921
20. Boscolo E, Limaye N, Huang L, et al. Rapamycin improves TIE2-mutated venous malformation in murine model and human subjects. *J Clin Invest* 2015;125:3491–3504
21. Hammer J, Seront E, Duez S, et al. Sirolimus is efficacious in treatment for extensive and/or complex slow-flow vascular malformations: A monocentric prospective phase II study. *Orphanet J Rare Dis* 2018;13:191
22. Salloum R, Fox CE, Alvarez-Allende CR, et al. Response of blue rubber bleb nevus syndrome to sirolimus treatment. *Pediatr Blood Cancer* 2016;63:1911–1914
23. McAllister KA, Grogg KM, Johnson DW, et al. Endoglin, a TGF-(binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. *Nat Genet* 1994;8:345–351
24. Eerola I, Boon LM, Mulliken JB, et al. Capillary malformation–arteriovenous malformation, a new clinical and genetic disorder caused by RASA1 mutations. *Am J Hum Genet* 2003;73:1240–1249
25. Revencu N, Boon LM, Mulliken JB, et al. Parkes Weber syndrome, vein of galen aneurysmal malformation, and other fast-flow vascular anomalies are caused by RASA1 mutations. *Hum Mutat* 2008;29:959–965
26. Amyere M, Revencu N, Helaers R, et al. Germline loss-of-function mutations in EPHB4 cause a second form of capillary malformation-arteriovenous malformation (CM-AVM2) deregulating RAS-MAPK signaling. *Circulation* 2017;136:1037–1048
27. Tan WH, Baris HN, Burrows PE, et al. The spectrum of vascular anomalies in patients with PTEN mutations: Implications for diagnosis and management. *J Med Genet* 2007;44:594–602
28. Couto JA, Huang AY, Konczyk DJ, et al. Somatic MAP2K1 mutations are associated with extracranial arteriovenous malformation. *Am J Hum Genet* 2017;100:546–554

29. Nikolaev SI, Vetiska S, Bonilla X, et al. Somatic activating KRAS mutations in arteriovenous malformations of the brain. *N Engl J Med* 2018;378:250–261
30. Konczyk DJ, Goss JA, Smits PJ, et al. Arteriovenous malformation associated with a HRAS mutation. *Hum Genet* 2019;138:1419–1421
31. Sudduth CL, McGuire AM, Smits PJ, et al. Arteriovenous malformation phenotype resembling congenital hemangioma contains KRAS mutations. *Clin Genet August* 2020doi:10.1111/cge.13833
32. Al-Olabi L, Polubothu S, Dowsett K, et al. Mosaic RAS/MAPK variants cause sporadic vascular malformations which respond to targeted therapy. *J Clin Invest* 2018;128:1496–1508
33. Goss JA, Huang AY, Smith E, et al. Somatic mutations in intracranial arteriovenous malformations. *PLoS One* 2019;14:e0226852
34. Goss JA, Konczyk DJ, Smits PJ, et al. Intramuscular fast-flow vascular anomaly contains somatic MAP2K1 and KRAS mutations. *Angiogenesis* 2019;22:547–552
35. Smits PJ, Konczyk DJ, Sudduth CL, et al. Endothelial MAP2K1 mutations in arteriovenous malformation activate the RAS/MAPK pathway. *Biochem Biophys Res Commun* 2020;529:450–454
36. Konczyk DJ, Goss JA, Smits PJ, et al. Malformation MAP2K1 mutation causes local cartilage overgrowth by a cell-non autonomous mechanism. *Sci Rep* 2020;10:4428
37. Edwards E, Phelps A, Cooke D. Monitoring arteriovenous malformation response to genotype-targeted therapy. *Pediatrics* 2020;146:e20193206
38. Lekwuttikarn R, Lim YH, Admani S, et al. Genotype-guided medical treatment of an arteriovenous malformation in a child. *JAMA Dermatol* 2019;155:256–257
39. Lindhurst MJ, Sapp JC, Teer JK, et al. A mosaic activating mutation in AKT1 associated with the proteus syndrome. *N Engl J Med* 2011;365:611–619
40. Amary MF, Damato S, Halai D, et al. Ollier disease and Maffucci syndrome are caused by somatic mosaic mutations of IDH1 and IDH2. *Nat Genet* 2011;43:1262–1265
41. Keppler-Noreuil KM, Sapp JC, Lindhurst MJ, et al. Clinical delineation and natural history of the PIK3CA-related overgrowth spectrum. *Am J Med Genet Part A* 2014;164:1713–1733
42. Keppler-Noreuil KM, Rios JJ, Parker VER, et al. PIK3CA-related overgrowth spectrum (PROS): diagnostic and testing eligibility criteria, differential diagnosis, and evaluation. *Am J Med Genet Part A* 2015;167:287–295
43. Kurek KC, Luks VL, Ayturk UM, et al. Somatic mosaic activating mutations in PIK3CA cause CLOVES syndrome. *Am J Hum Genet* 2012;90:1108–1115
44. Maclellan RA, Luks VL, Vivero MP, et al. PIK3CA activating mutations in facial infiltrating lipomatosis. *Plast Reconstr Surg* 2014;133:12–19
45. Couto JA, Konczyk DJ, Vivero MP, et al. Somatic PIK3CA mutations are present in multiple tissues of facial infiltrating lipomatosis. *Pediatr Res* 2017;82:850–854
46. Mirzaa GM, Rivière JB, Dobyns WB. Megalencephaly syndromes and activating mutations in the PI3K-AKT pathway: MPPH and MCAP. *Am J Med Genet Part C Semin Med Genet* 2013;163:122–130
47. Parker VER, Keppler-Noreuil KM, Faivre L, et al. Safety and efficacy of low-dose sirolimus in the PIK3CA-related overgrowth spectrum. *Genet Med* 2019;21:1189–1198
48. Venot Q, Blanc T, Rabia SH, et al. Targeted therapy in patients with PIK3CA-related overgrowth syndrome. *Nature* 2018;558:540–546
49. López Gutiérrez JC, Lizarraga R, Delgado C, et al. Alpelisib treatment for genital vascular malformation in a patient with congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and spinal/skeletal anomalies and/or scoliosis (CLOVES) syndrome. *J Pediatr Adolesc Gynecol* 2019;32:648–650