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Mini review

Molecular genetics of vascular malformations

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Abstract

Vascular malformations are *localized* errors of angiogenic development. Most are cutaneous and are called vascular 'birthmarks'. These anomalies are usually obvious in the newborn, grow commensurately with the child, and gradually expand in adulthood (Mulliken and Glowacki, 1982). Vascular malformations also occur in visceral organs, such as the respiratory and gastrointestinal tract, but are more common in the brain (Mulliken and Young, 1988). These anomalies are composed of tortuous vascular channels of varying size and shape, lined by a continuous endothelium and surrounded by abnormal complement of mural cells. Vascular malformation can be life threatening due to obstruction, bleeding or congestive heart failure. Most anomalies occur sporadically, but there are families exhibiting autosomal dominant inheritance. Genetic studies of such families have resulted in the identification of mutated genes, directly giving proof of their important role in the regulation of angiogenesis.

Keywords: TIE2; VEGFR3; Angioprotein; KRIT1; Vascular anomaly; Glomus tumor; Angiogenesis; Cavernous angioma; Hemangioma; Arterio-venous malformation; Lymphedema; Glomuvenous malformation; Venous malformation

1. Introduction

Cutaneous vascular lesions all look very similar at first glance, but there are important clinical and histologic differences. The pattern of growth is a critical determinant in differential diagnosis. *Vascular malformations* enlarge very slowly, commensurately with the growth of the child. In contrast, the most common vascular *tumors*, hemangiomas, grow rapidly during the first year of life and spontaneously regress over the ensuing 1–8 years (Mulliken and Glowacki, 1982; Mulliken and Young, 1988). Histologically, hemangiomas are composed of tightly packed sinusoidal channels, lined by plump rapidly dividing endothelial cells. In contrast, vascular malformations are composed of abnormal channels, and the lining endothelium is quiescent. On the basis of their clinical appearance, natural history, and histopathology, vascular malformations are divided into arterio-venous, capillary, lymphatic, venous and combined lesions (Mulliken and Glowacki, 1982). Vascular malformations are developmental defects, probably caused by dysregulation in signaling that regulates proper formation of the vascular tree. Hemangiomas are tumors that express a localized increase in angiogenic growth factors. These differences are supported by the identification of mutated genes that cause specific inherited forms of

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venous, arteriovenous and capillary-venous malformations, as well as lymphedema.

2. Venous malformation

Venous malformations (VM) are the most common vascular anomalies seen in referral centers (Fig. 1). Most VMs are cutaneous and intramuscular, but they can occur in any organ. The incidence is not known, but we assess the range to be between 1/5000 and 1/10 000 births. The lesions range in size from very small to extensive. VMs can be flat or raised. They are violaceous to bluish in color, due to stagnation of venous blood within the lesion (Enjolras et al., 1990). Multifocal lesions occur, and this finding is often a clue to a familial predisposition (Boon et al., 1994; Gallione et al., 1995). Recanalization and recurrence commonly occur after sclerotherapy and/or incomplete resection.

Histological sectioning of a VM reveals convoluted vascular channels of variable size and thickness. The venous spaces often fill most of the microscopic slide. The surrounding extracellular matrix appears normal in VM (Mulliken and Glowacki, 1982). PCNA (proliferating cell nuclear antigen) staining was negative for endothelial cells in VMs from a 1.5- and 11-year-old patient (Takahashi et al., 1994; Kräling et al., 1996). In addition, H^3-thymidine uptake was not observed in VMs (Mulliken and Glowacki, 1982). Angiogenic markers, such as VEGF, bFGF, and TIMP1 showed low expression in an 11-year old child's VM (Takahashi et al., 1994). Interestingly, this lesion was negative for the universal endothelial marker CD31 (Takahashi et al., 1994). In our studies, we noted a relative lack of smooth muscle cells in inheritable VMs (Vikkula et al., 1996). This could be explained as either the result of overproliferation of endothelial cells or lack of recruitment of smooth muscle cells. Both phenomena could be caused by changes in intra- or intercellular signaling or indirectly, by changes in the extracellular matrix (Vikkula et al., 1998).

By studying a large family with inherited VMs, we discovered a locus on the short arm of chromosome 9 that linked to the phenotype (Boon et al., 1994) (Table 1). With the help of collaborators, we found another family that also showed linkage to this region (Gallione et al., 1995). Using positional cloning and candidate gene analyses, we demonstrated that the cause for VMs in these two families was a mutation in the gene encoding the endothelial specific receptor tyrosine kinase TIE2, the angiopoietin receptor (Vikkula et al., 1996). Interestingly, the mutation in both families was exactly the same: a one amino acid substitution, R849W, in the intracellular kinase domain. As the allele linked to the mutation was different in the two families, these mutations were likely to have originated independently (Vikkula et al., 1996). This suggested that either the mutations occur in a 'hotspot' in this gene or that only few changes in the receptor can alter its function to cause venous anomalies. The first possibility is supported by the

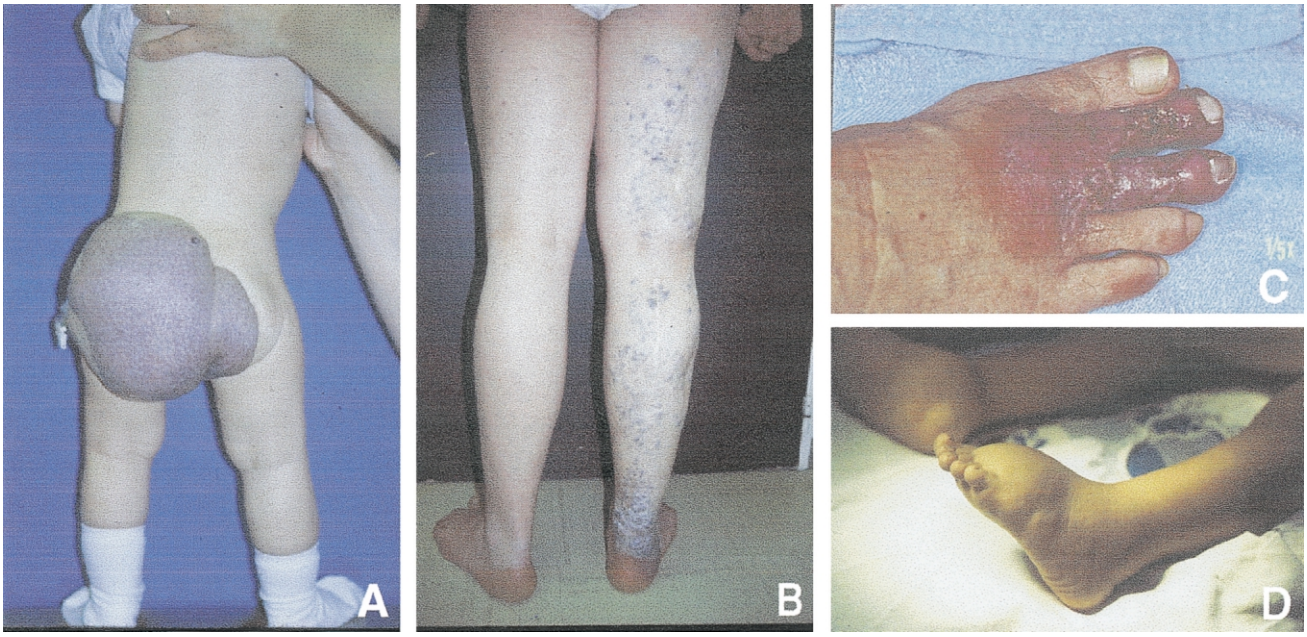

Fig. 1. (A) Large venous malformation (VM) of buttock, (B) extensive glomuvenous malformation (GVM) of right leg (note the bluish-violaceous color, cobblestone appearance and hyperkeratosis, especially at ankle), (C) ulcerated arteriovenous malformation (AVM) of the distal foot, and (D) lymphedema of foot.

Table 1
Characteristics of vascular malformations

Vascular malformation	Inheritance	Penetrance	Chromosome/gene	Mutation type	Clinical features/histology
I. Arteriovenous malformation (AVM)	Somatic mutations?	?	?	?	Intermixed dysmorphic arterial and venous-like channels with direct connections
II. Arteriovenous malformation (AVM) in hereditary hemorrhagic telangiectasia					
HHT1	AD	Approximately 100%	9q33–34/endoglin	Loss of function	Direct anastomoses between arterioles and arteriolized venules
HHT2	AD	Approximately 100%	12q11–14/activin like receptor-tyrosine kinase	Loss of funcion	
III. Capillary malformation (CM)	AD?	?	?	?	Convoluted dilated dermal capillary-sized channels with thin walls
IV. Cutaneous capillary-venous malformation associated with CCM (HCCVM)	AD	40%	7q11.2-q21/KRIT1	Loss of function	Convoluted dilated dermal capillary-sized channels (with thin walls) and venous-like channels (with thick fibrotic walls)
V. Cerebral cavernous malformation (CCM)					
CCM1	AD	88%	7q11.2-q21/KRIT1	Loss of function?/ dominant negative	Convoluted dilated dermal capillary-sized channels (with thin walls) and venous-like channels (with thick fibrotic walls)
CCM2	AD	100%	7p15–p13/?	?	
CCM3	AD	63%	3q25.2–q27/?	?	
VI. Lymphatic malformation (LM)	Somatic mutations?	?	?	?	Convoluted dilated lymphatic vessels with thin walls
VII. Lymphedema, congenital	AD	< 100%	5q35.3/VEGFR3	Loss of function	Hypoplasia/aplasia of the lymphatic vasculature
	AR?	?	?	?	
	X-linked	?	?	?	
VIII. Lymphedema, praecox	AD	< 100%	?	?	
IX. Lymphedema with distichiasis	AD	< 100%	16q24.3/?	?	With abnormal hairs from Meibomian glands
X. Venous malformation (VM)					Convoluted dilated venous-like channels
Cutaneomucosal (VMCM)	AD	94%	9p21–22/TIE-2	Gain of function	lacking smooth muscle
With 'glomus cells' (VMGLOM)	AD	Approximately 100%	1p21–22/?	?	with surrounding glomus cells

AD = Autosomal dominant.
AR = Autosomal recessive.
? = Not known.

identification of a third family that carries exactly the same mutation (Calvert et al., 1999). On the other hand, a different mutation, Y897S, located in the same kinase domain, has been identified in a fourth family (Calvert et al., 1999).

As both TIE2 mutations are single amino acid substitutions, their effect on receptor function is not obvious. Therefore, we used recombinant mutant human TIE2 to examine autophosphorylation and signaling in vitro. Uninduced overexpression studies showed that the level of autophosphorylation of the mutant receptor was 6–10 times higher than for the wild-type receptor (Vikkula et al., 1996). Thus, the mutant receptor has not lost its signaling capacity; instead, it signals more strongly. Furthermore, we demonstrated differences in the intracellular signaling capacity of the mutant TIE2 by co-transfecting 293T cells with mutant and wild-type TIE2 with STAT1, 3 and 5 (signal transducer and activator of transcription) (Korpelainen et al., 1999). Mutant TIE2 phosphorylates STAT3 and STAT5 more strongly than the wild-type receptor. In addition, mutant TIE2 activated STAT1 and, thereby, expression of p21 and a related transcript (Korpelainen et al., 1999) (Fig. 2). These findings suggest that some of the phenotypic effects caused by the mutant TIE2 receptor are due to changes in control of the endothelial cell cycle, leading to a relative deficiency of smooth muscle cells.

The signaling cascade downstream of TIE2 is complex. Several substrates have been identified, such as Shp2, PI3K, Dok-R, and GRBs 2, 7 and 14 (Huang et al., 1995; Jones and Dumont, 1998; Kontos et al., 1998; Jones et al., 1999) (Fig. 2). These molecules point to specific signaling pathways downstream of the receptor. However, it is unclear, what molecular changes are caused by TIE2 activation in these pathways and how they are disrupted by mutant TIE2 activation. Cell culture experiments have shown that

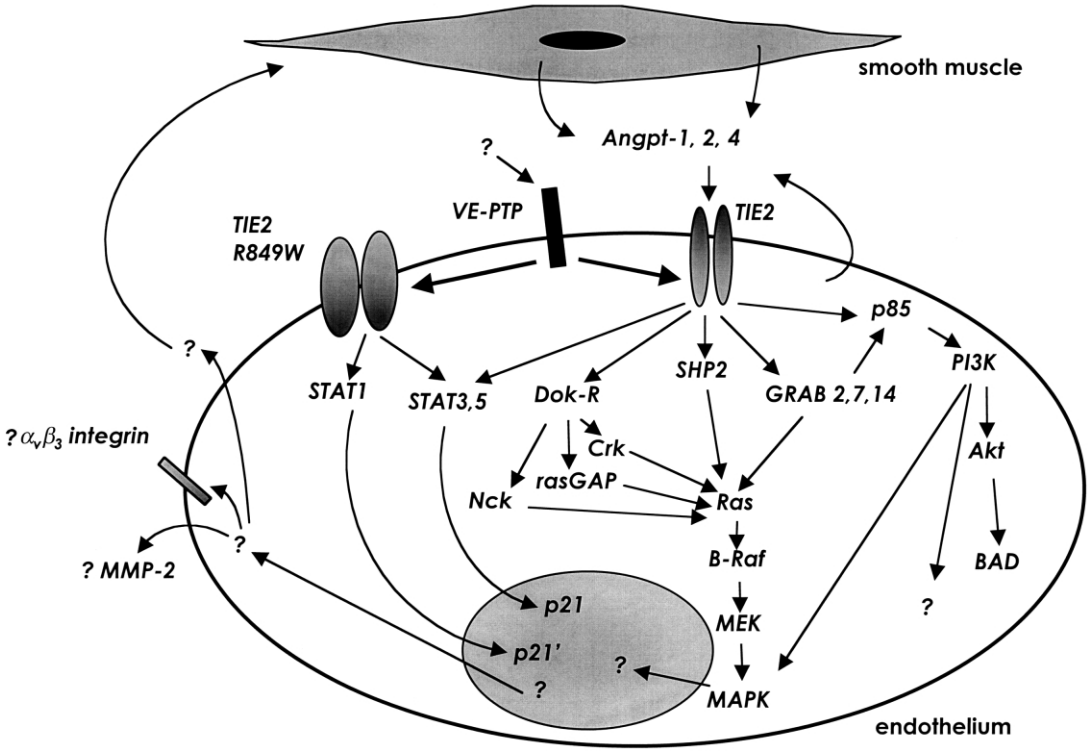

Fig. 2. Schematic representation of possible signaling via TIE2, vascular endothelial-specific receptor tyrosine kinase. Top, a smooth muscle cell, and bottom, an endothelial cell. Three TIE2 ligands (angiopoietins) marked: Angpt1; 2; and 4, possibly secreted by smooth muscle cells and endothelial cells. Receptor-type vascular endothelial protein–tyrosine-phosphatase (VE–PTP) specifically interacts with TIE2, marked with a rectangular black box. VE–PTP ligand unknown. Wild-type and R849W mutant TIE2 receptors represented as homodimers. R849W TIE2 represented by thick ovals. Arrows from R849W TIE2 towards all possible substrates of wild-type TIE2 omitted for clarity. Eight identified possible TIE2 substrates shown: STAT3 and STAT5 (signal transducers and activators of transcription); Dok-R (downstream of tyrosine kinase-related); Shp2 (SH2 tyrosine phosphatase); Grb2, Grb7 and Grb14 (growth factor receptor-bound protein); and p85/P13-kinase (phosphatidylinositol 3-kinase). In addition, STAT1, activated by R849W TIE2, represented. Selected effectors, downstream of possible TIE2 substrates, also shown. p21 = cyclin-dependent kinase inhibitor 1A (CDKN1A) also known as WAF1, refers to increased transcription observed after TIE2 induction; p21′, a putative homologous transcript. Akt = a serine–threonine protein kinase; BAD = Bcl2 antagonist of cell death; Nck = melanoma adaptor protein; rasGAP = ras GTPase-activating protein; Crk = oncogene with src-homology domains; Ras = 21 kDa, small GTP-binding protein; B-Raf = a 94-kDa serine–threonine kinase; MEK = MAPK kinase; MAPK = mitogen-activated protein kinase; and MMP-2 = matrix metalloproteinase 2.

TIE2, via Angpt1 (angiopoietin 1), plays an important role in endothelial cell survival and migration (Witzenbichler et al., 1998; Jones et al., 1999; Kim et al., 2000; Papapetropoulos et al., 2000). TIE2 may also be associated with secretion of matrix metalloproteinases (Kim et al., 2000). In addition, Angpt1-induced cellular adhesion of TIE2 positive hematopoietic cells is partially blocked by antibodies against β_1 integrin (Takakura et al., 1998). Thus, the histological appearance of VMs could reflect changes in extracellular matrix and/or adhesion.

Important data on the developmental importance of Tie2 has been obtained from murine studies. Mice null for Tie2, or its ligand Angpt1, die around E9.5, due to disruption of embryonic angiogenesis (Dumont et al., 1994; Sato et al., 1995; Suri et al., 1996). A slightly more severe phenotype was seen with overexpression of the competing 'inhibitory' ligand angiopoietin 2 (Angpt2) (Maisonpierre et al., 1997). Furthermore, overexpression of Angpt1 in the skin caused vascular hyperplasia (Suri et al., 1998). Thus, TIE2 and its ligands are crucial for proper vascular development, and lack of or overactivity of this signaling pathway disrupts vascular morphogenesis.

Of interest, a venous specific phenotype was not found in the engineered mice, whereas patients carrying TIE2 mutations only develop localized *cutaneomucosal venous* anomalies. As these patients are heterozygous for the dominant mutation, a somatic second hit might be necessary to produce lesions. On the other hand, the occurrence of localized lesions could result from stochastic events that determine cellular faith and thus, the direction of development. The fact that these are venous lesions only is also intriguing because expression of TIE2 occurs in other types of blood vessels (Dumont et al., 1995; Schlaeger et al., 1997). This venous localization may be explained by the protective effect of the vascular endothelial-protein–tyrosine phosphatase that is specific for TIE2 and exhibits lower expression in capillaries and small veins (Fachinger et al., 1999). It remains to be determined whether this is the only factor influencing the location of venous malformations, and thus, being a possible molecular site for therapeutic intervention.

3. Glomuvenous malformation (venous malformation with 'glomus cells')

Glomuvenous malformations (GVM), or venous malformations with 'glomus cells', are a subtype of venous anomalies (Fig. 1). Usually, these lesions can be clinically differentiated from the more common VMs (Boon et al., in preparation). GVM lesions are raised, bluish-purple, with a cobblestone surface. They are very painful on palpation. They are rarely encountered in mucous membranes, in contrast to other VMs which commonly occur in buccal and intestinal mucosa, and in other organs (Boon et al., 1994; Vikkula et al., 1995).

The pathognomonic finding in GVM is 'glomus cells' around the convoluted venous-like channels. Their number varies greatly between different lesions, as well as within different areas of the same lesion. The term 'glomus' (a ball or sphere) comes from the morphologically similar contractile cells in the Sucquet–Hoyer arteriovenous anastomoses of glomus bodies that are involved in cutaneous thermoregulation (Pepper et al., 1977). Glomus cells have rounded nuclei, express smooth muscle cell markers such as α-actin and vimentin, and have ultrastructural characteristics of smooth muscle cells (Pepper et al., 1977; Dervan et al., 1989; Boon et al., 1999). Glomus bodies do not contain elastic tissue, whereas glomuvenous malformations sometimes have elastic fibers (Gupta et al., 1965). Thus, glomus cells in GVM are most likely modified smooth muscle cells.

Our genetic studies corroborate the clinical and histological differences between VMs and GVMs. The majority of GVMs are inherited, and we have been able to collect blood samples from several affected families. Linkage analysis in five families identified a novel locus, *VMGLOM*, on the short arm of chromosome 1 (Boon et al., 1999) (Table 1). Characterization of seven additional families with inherited GVMs showed linkage disequilibrium in this region among a subset of families. This enabled us to narrow the region to a single 1.48-Mpb YAC (Irrthum et al., 2001). By mutation screening, we excluded the most likely candidate genes in the locus (Boon et al., 1999) and thus, generated a physical and transcript map of the region for positional cloning (Brouillard et al., 2000). Ongoing efforts are aimed at identification of the mutated gene.

There are no genes known to be involved in vascular morphogenesis in the narrowed *VMGLOM* region. Thus, the mutated gene must be a novel factor regulating vasculogenesis and/or angiogenesis. It is of interest whether it acts in TIE2 signaling or in concert with TIE2 as VMs have a relative deficiency of smooth muscle cells and GVMs have a variable abundance of modified smooth muscle cells. Its identification would also help understand the mechanism of development of venous anomalies, thought to be due to weakened mural support.

4. Arteriovenous malformation

The most dangerous vascular anomalies are high-flow arteriovenous malformations (AVM) (Fig. 1) and arteriovenous fistulae (AVF). They occur sporadically

and manifest, as red, warm, pulsatile cutaneous lesions (Mulliken and Young, 1988). AVMs are perhaps most common in the central nervous system, where they present insidiously or suddenly with neurologic consequences. Histologically, AVM is composed of dysplastic arteries intermingled among arterialized veins with thickened intimal lining. Endothelium, cultured from AVMs, has shown increased growth and reduced apoptosis, suggesting an intrinsic cellular defect (Wautier et al., 1999).

Cutaneous AVMs are not believed to be inheritable, but AVMs are part of hereditary hemorrhagic telangiectasia (HHT), where they typically arise in lungs, brain, and sometimes in the gut (Guttmacher et al., 1995) (Table 1). Two genes encoding TGFβ receptor associated proteins, endoglin and activin receptor-like kinase I, have been identified to cause *HHT1* and *HHT2,* respectively, (McAllister et al., 1994; Johnson et al., 1996) (Table 1). They are both expressed in endothelial cells (Gougos and Letarte, 1990). Endoglin is an accessory protein of TGFβ receptor complexes, incapable of binding TGFβ alone. Activin receptor-like kinase I is a transmembrane serine/threonine kinase that can bind TGFβ (Attisano et al., 1993; Barbara et al., 1999). The numerous mutations identified in these genes cause loss-of-function of the encoded proteins, and a lack of TGFβ signaling occurs. Thus, it seems that TGFβ is important for normal arteriovenous differentiation and/or maintenance of normal capillaries. The latter seems more likely, as it is believed that a progressive disappearance of the capillary bed occurs during development of cutaneous telangiectasias in HHT (Guttmacher et al., 1995).

Despite the lack of TGFβ in telangiectasias, smooth muscle cell proliferation occurs in the postcapillary venules in these lesions. Thus, lack of TGFβ does not seem to influence recruitment of supporting cells. Genetically engineered mice, particularly mice heterozygous for an endoglin null-allele, suggest that epigenetic factors, which influence the phenotype, exist as only some animals exhibit cutaneous telangiectasias and epistaxis (Bourdeau et al., 1999). These mice are a close phenocopy of HHT patients who have multiple *localized* lesions.

Thus, it is clear that derangements in TGFβ signaling are involved in formation of AVMs, but only in HHT. Cutaneous AVMs are uncommon in HHT patients. Interestingly, PTEN (dual-specificity phosphatase) was shown to be mutated in a sporadic patient with a 'Proteus-like' syndrome, characterized by massive hypertrophy of the right lower extremity, lipomas, macrocephaly and extensive AVMs involving both lower extremities, pelvis, lower abdomen and buttocks (Zhou et al., 2000). This patient had a de novo germline non-sense mutation, as well as a somatic or germline mosaic non-sense mutation. Thus, the affected tissues totally lack PTEN. This same gene has been shown to be mutated in Cowden syndrome and Banayan–Riley–Ruvalcaba syndrome, two hamartoma-tumor syndromes, and is considered a tumor suppressor gene. The cause of the extensive AVM in this patient could be uncontrolled endothelial proliferation leading to abnormal vascular connections and thus, PTEN signaling could be involved in cutaneous AVMs. To evaluate the role of the factors involved in TGFβ and PTEN signaling, as well as other possible causes, studies on resected cutaneous AVMs are needed.

5. Cutaneous and cerebral capillary-venous malformation

Although most vascular anomalies are cutaneous, capillary-venous malformations have a predilection for brain. In the past, these lesions were called either 'cavernoma' or 'cavernous angioma'; now the more precise term 'cerebral cavernous malformation' (CCM) is preferred. These localized intracerebral lesions cause seizures, hemorrhage, and headaches (Giombini and Morello, 1978). Histologic sections vary between different areas of a lesion as well as between lesions in the same patient. Typically, CCM is composed of large vascular lumens with thickened fibrotic walls and surrounded by brain parenchyma. Alternatively, there are small, capillary-like vascular spaces, with walls composed of a single endothelial cell layer (Fig. 1). There is no parenchyma surrounding these malformed vessels, thus giving a honeycomb or lace-like appearance to this vascular anomaly (Rigamonti et al., 1991). Immunohistochemistry revealed lack of laminin and pericytes in these vessels (Robinson et al., 1995). In addition, newly formed lesions have a lacey appearance and endothelial cells in these capillary malformations are proliferative, as shown by PCNA staining (Notelet et al., 1997). Older lesions tend to contain larger vessels with fibrotic walls. Thus, CCMs may be due to continuos abnormal angiogenesis or intralesional hemorrhage with reactive capillary proliferation.

There are numerous families with autosomal dominantly inherited cerebral capillary-venous malformations, especially Hispanic Americans (Mason et al., 1988; Rigamonti et al., 1988). Genetic analyses have detected three chromosomal loci: *3q25.2-q27; 7p15-13;* and *7q11.2-q21* (Dubovsky et al., 1995; Craig et al., 1998) (Table 1). Positional cloning was used to identify the mutated gene in the *CCM1* locus on 7q. This gene, *KRIT1* (Krev1 interaction trapped 1), was originally discovered by a yeast two-hybrid system as a protein that interacts with Krev1/Rap1A, a molecule

participating in Ras signaling (Serebriiskii et al., 1997). However, its function is unknown. As many of the identified mutations caused premature STOP codons in the *KRIT1* open reading frame, it is assumed that they cause loss-of-function (Laberge-le Couteulx et al., 1999; Sahoo et al., 1999; Eerola et al., 2000; Zhang et al., 2000). Thus, CCM could result from dysregulation of Ras-controlled endothelial cell proliferation.

Although Northern hybridization showed that *KRIT1* is strongly expressed in the brain, a transcript was also found in many other tissues (Laberge-le Couteulx et al., 1999). The functional significance for this wide expression was better understood after identification of a KRIT1 mutation causing inherited *cutaneous* capillary-venous malformations (CVMs) in association with CCM (Eerola et al., 2000) (Table 1). These localized reddish-blue cutaneous lesions are characterized by combined capillary-venous channels (Labauge et al., 1999; Eerola et al., 2000). Thus, *KRIT1* is not only important for cerebral angiogenesis but for evolving cutaneous vessels as well.

Like other vascular malformations, CCMs and CVMs are localized and affect only certain vascular types. Thus, we speculate that a second somatic hit is needed to cause the lesion (Knudson's double-hit hypothesis for retinoblastoma). This would make sense in cases of CCM and CVMs, for which the inherited mutation causes loss-of-function. A somatic hit, causing mutation in the wild-type allele, could result in complete local loss of *KRIT1*. Until mutated genes in *CCM2* and *CCM3* are known, it is impossible to fully understand the etiopathogenesis of these lesions.

6. Lymphedema

Lymphedema is the term used to describe diffuse, subcutaneous swelling, usually involving the lower extremities (Fig. 1). Generalized lymphedema is uncommon. The condition can be congenital (Milroy disease); however, 80% of cases are late-onset (Meige disease) (Mangion et al., 1999) (Table 1). By lymphangiography, lymphedema is characterized by aplasia, hypoplasia, or hyperplasia of lymphatic channels. Lymphedema has strong familial aggregation, up to 35% of patients have a positive family history (Dale, 1985).

Linkage analysis has revealed at least two separate chromosomal loci linked to inherited lymphedema: chromosome *5q35.3* for congenital lymphedema, and *16q24.3* for lymphedema with distichiasis (hairs raising from inner eyelid Meibomian glands) (Ferrell et al., 1998; Mangion et al., 1999) (Table 1). We studied a two-generation family with five individuals affected with congenital lymphedema. The family showed linkage to *5q35*, where the *VEGFR3* gene (vascular endothelial growth factor receptor 3, also called *FLT4*) is located. As *VEGFR3* expression is known to be restricted to lymphatic endothelium during embryogenesis (Kaipainen et al., 1995), we decided to screen it for possible mutations. We identified a single nucleotide transition that resulted in H1035R substitution in the well-conserved catalytic loop of the intracellular kinase domain of the receptor (Irrthum et al., 2000). Concurrently, five other substitutions were described (Karkkainen et al., 2000). Co-transfection experiments in 293T cells for autophosphorylation activity of these six mutations showed no signal with the mutant receptors (Irrthum et al., 2000; Karkkainen et al., 2000). Thus, congenital lymphedema, linked to *5q35*, seems to be caused by lack of sufficient signaling via the VEGFR3 receptor. Whether the mutant-receptors have dominant-negative effects in vivo, cannot be excluded. Such an affect is possible as mice heterozygous for null-allele of *VEGFR3* do not exhibit vascular or lymphatic phenotype (Dumont et al., 1998), as expressed by heterozygous patients carrying a dominant mutation. This could also be explained by differences between murine and human physiology, and by the requirement of total local loss of VEGFR3 by a 'second hit' somatic mutation.

7. Conclusions

Vascular malformations of the skin and other organs are intriguing examples of developmental dysmorphogenesis. Their diversity reflects the multiple factors involved in the proper regulation of vasculogenesis and angiogenesis. Molecular discoveries have indicted genes expressed in endothelial cells and involved in receptor signaling (Table 1). These mutated genes encode tyrosine kinase receptors and intracellular signaling molecules. There may also be a role for extracellular matrix components in the evolution of vascular anomalies. For example, endothelial-to-smooth muscle cell signaling could occur via extracellular matrix. This is corroborated by the fact that there are differences in supporting cells for venous and capillary-venous anomalies.

Traditional strategies for treatment of vascular anomalies are based on destroying the vascular spaces, using laser or intralesional injection of sclerosing agents, and surgical resection. Identification of causative genes opens the door to biologic therapy. Transgenic animal models could be used to identify modifying factors, evaluate novel treatments, and devise ways to prevent evolution of a vascular malformation. Animal models of vascular anomalies will also facilitate the study of molecular pathways controlling vasculogenesis and angiogenesis. Already, VEGF and

angiopoietin are known to be associated with developmental as well as tumor-induced angiogenesis. Other common disorders involving dysregulation of vascular growth could be due to deranged signaling. Thus, identification of these genes could expose therapeutic targets for a wide range of angiogenic disorders.

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