Etiology and Genetics of Congenital Vascular Lesions

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KEYWORDS

• Malformation • Vascular • Gene • Mutation • Signaling pathway • Inhibitor • Rapamycin

KEY POINTS

- Therapeutic options to treat vascular tumors and malformations are limited. Detection of genetic mutations, inherited or somatic, has opened up the field for understanding the underlying molecular mechanisms.
- RAS/MAPK/ERK signaling is increased because of mutations in *GNAQ* and *GNA11* in congenital hemangiomas and capillary malformation (CM), in *GNAQ*, *KRAS* and *BRAF* in pyogenic granuloma (PG), in *RASA1* in CM-AVM1, in *EPHB4* in CM-AVM2, in *KRIT1* in HCCVM, and in *MAP3K3* in verrucous venous malformations.
- PI3K/AKT/mTOR pathway is increased in hereditary hemorrhagic telangiectasia (HHT) with mutations in *BMP9/10*, *ALK1*, and *endoglin*, in sporadic venous malformations (VM and MVM), and blue rubber bleb nevus syndrome (BRBN), inherited cutaneomucosal venous malformations (VMCM), all with mutations in *TIE2*, and in sporadic VM and lymphatic malformations (LM) with mutations in *PIK3CA*.
- Increased hepatocyte growth factor/c-Met and TGF-ß signaling may occur in glomuvenous malformations (GVM) with mutations in *glomulin*.
- VEGFR1 expression is decreased and VEGF-A/VEGFR2 signaling is increased in infantile hemangioma (IH) with mutations in *TEM8* and *VEGFR2*.

INTRODUCTION

Lesions of the vascular system are the most common congenital and neonatal abnormalities.[1] Vascular malformations of the head and neck region constitute approximately 60% of the lesions and occur approximately in 1 out of 22 children.[2]

Disclosure: The authors have nothing they wish to disclose.
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Otolaryngol Clin N Am 51 (2018) 41–53
https://doi.org/10.1016/j.otc.2017.09.006 **oto.theclinics.com**

Mulliken and Glowacki[3] laid out the foundation for a clear classification based on physical findings, clinical behavior, and cellular kinetics. Vascular anomalies are separated into two major categories: vascular tumors (mainly hemangiomas [congenital and infantile] and other vascular tumors) and vascular malformations (named according to the affected type of vessel: capillary, venous, lymphatic, arteriovenous, and mixed malformations).[3] Most types are known to be caused by inherited and/or somatic mutations. It is hoped that further studies on cellular effects of the mutations will lead to a better understanding of the underlying pathophysiology enabling development of novel treatments.

VASCULAR TUMORS

Etiology and Genetics of Hemangiomas

Congenital hemangioma

Congenital hemangiomas are rare lesions, and fully formed at birth.[2,4] There are three types: (1) rapidly involuting (RICH), (2) partially involuting, and (3) noninvoluting congenital hemangioma (NICH).[5] They do not express the glucose transporter-1 protein (GLUT1).[2]

Mutually exclusive, mosaic missense mutations in *GNAQ* and *GNA11* at position glutamine 209 (Gln209) have been identified.[6,7] *GNAQ* encodes the guanine nucleotide binding protein G(q) alpha, a subunit within a complex that hydrolyzes GTP to GDP.[6] The same somatic mutations have been reported in more than 80% of uveal melanomas.[8] In them, Gln209 missense mutations activate GTP-dependent signaling leading to constitutive activation of MAPK and/or YAP signaling.[6] These pathways may also be involved in RICH and NICH (**Fig. 1**).

Pyogenic granuloma

Pyogenic granuloma (PG) is a common benign vascular neoplasm and its occurrence within a capillary malformation (CM; see later) is a well-recognized event.[1,9] In such secondary PGs, a somatic GNAQ p.Arg183Gln mutation is present, reflecting an origin from cells of the underlying CM.[9] Moreover, 8 out of 10 secondary PGs have a BRAF p.Val600Glu somatic mutation and 1 out of 10 an NRAS p.Gln61Arg mutation. In contrast, in isolated PG, BRAF p.Val600Glu (in 3 of 25 cases) or p.Gly464Glu mutations or KRAS p.Gly13Arg (in 1 of 25) mutations were detected.[9] Therefore, it is speculated that the BRAF p.Val600Glu mutation is a driver event in isolated PGs, and a second-hit on a GNAQ p.Arg183Gln mutated CM-background in secondary PG.[9] Furthermore, mutations in *HRAS*, also identified in patients with colon cancer, play a role in PG (p.Q61R, p.E49K, Q61R, and p.G13S).[10] In summary, upregulated RAS/MAPK signaling seems to be the key mechanism (see **Fig. 1**, **Box 1**).

Infantile hemangioma

Infantile hemangioma (IH) ensues from endothelial cell (EC) hyperplasia. The cause of the aberrant EC proliferation remains unknown.[11] There are two theories: involvement of embolic placental angioblasts based on sharing of placental markers, such as GLUT1, Lewis Y antigen, and merosin; and Fcγ receptor II, with hemangiomas.[12] The embryonic endothelial precursor theory is based on detection of $CD133^+$/$CD34^+$ circulating progenitor and stem cells in hemangiomas and blood circulation of patients with hemangioma.[13] Moreover, injection of such "hemangioma stem cells" into nude mice led to development of hemangioma-like lesions.[14]

Vascular endothelial growth factor (VEGF)-A signaling seems to be a key in IH because changes in VEGF-A signaling pathway in hemangioma ECs leads to the formation of IH.[15] Sequencing 24 genes involved in EC proliferation, migration, adhesion, or