Vasculopathy: a possible factor affecting hereditary angioedema

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ABSTRACT

Hereditary angioedema (HAE) is a rare genetic disorder that causes swelling of tissues in the hands, feet, limbs, face, intestinal tract, or airway. The SERPING1 gene, encoding the C1-INH, determines the wide range of clinical symptoms associated with CI-INH deficient HAE. C1-INH regulates enzymes involved in bradykinin production, leading to increased vascular permeability and angioedema. The most prevalent cause of this condition is either a deficiency or dysfunction of C1-INH. A subset of patients exhibits a third form of HAE (nC1-INH-HAE). This clinical subtype, distinguished by the absence of mutations in SERPING1, has a clinical picture similar to C1-INH-HAE but with normal C1-INH level and activity. This review summaries recent progress in genetic characterization of angioedema and discusses future potential for identifying additional genetic abnormalities in HAE. The elucidation of mechanisms leading to HAE could contribute to better understanding of the endothelial cell physiopathology.

Introduction

Angioedema (AE) is characterized by a localized, self-limiting, and transient subcutaneous or submucosal swelling, which can present with or without episodes of urticaria, and usually subsides within 24-37 h. Based on the history, physical examination, and laboratory tests, the possible classifications include drug-induced angioedema, hereditary angioedema, or acquired angioedema.[1] According to the American Academy of Allergy Asthma and Immunology, AE is characterized by "swelling of the lower layer of skin and tissue just under the skin or mucous membranes" and causes recurrent attacks of severe swelling, primarily affecting the arms, legs, face, genitalia, intestinal tract, airway, and lips.[2] HAE is an autosomal dominant condition with reported prevalence 1:100,000. It was first documented in 1888 by Canadian physician William Osler and is observed to have a more severe impact in women than in men.[3] HAE commonly presents with symptoms starting in childhood and worsening during puberty. If left untreated, individuals usually have an attack every one to two weeks, lasting three to four days on average. Except for patients with abdominal swellings who often experience severe abdominal pain, some may encounter a feeling of fullness without pain or itching in the affected area. Others may undergo intense pain that radiates outward from the bone, accompanied by severe heat and intense itching just beneath the skin. Swelling in the digestive and respiratory systems can lead to significant risk and discomfort. Involvement of respiratory structures, such as the throat or larynx, can result in breathing problems and potentially fatal airway obstruction.[4] Complications arising from episodes impacting the gastrointestinal tract may involve diarrhea, abdominal cramping, vomiting, and dehydration.[5] A small proportion of individuals experience "wandering" attacks, where the focal point of the attacks is an extremity, i.e. they will go through the typical swelling cycle before "transferring" to the other extremity or the connecting limb (such as the forearm, from the wrist). This symptom can prolong episodes and make it more difficult to identify triggers. Around one-third of cases involve a prodromal rash, and other prodromal symptoms such as tingling, weakness, or fatigue at the site of imminent edema seem to occur in some individuals.[4,6] In contrast to other causes of angioedema, such as symptoms induced by histamine, urticaria is typically absent from HAE. Without prophylactic care, attacks typically reoccur, also every two weeks, and last for several days. Clinical manifestations vary widely, from no symptoms in some individuals to others experiencing severe, life-threatening attacks with significant economic and human costs.[7] The clinical description, identification of attack triggers, response to medication during an acute episode, and any relevant family history all contribute to the diagnosis. Although there have been sporadic descriptions of neurologic symptoms, case series and case reports analyzed the literature currently avail-

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able for this uncommon clinical presentation.[8] Even within the same family, individuals with HAE vary significantly in the frequency and duration of their attacks. Attacks can be triggered by small trauma or stress, but they frequently happen in the absence of any clear precursory events. In the absence of therapy, there is a roughly 25% chance of death when the airway is affected. Results from treatment are usually favorable.

Classification: C1-INH-HAE type I, C1-INH-HAE type II, and nC1-INH-HAE

HAE is characterized by considerable genetic heterogeneity. The most prevalent cause of this condition is either a deficiency in or a malfunctioning of the C1 esterase inhibitor gene (*C1-INH*). The serpin family G member 1 (*SERPING1*) gene encodes for the C1-INH, an inhibitor of complement factor 1. The serine protease inhibitor C1-INH is a member of the sizable serine protease inhibitor (serpin) superfamily. This multispecific protease inhibitor is found in normal human plasma and serum. C1-INH modulates the activity of several enzymes in the complement system, coagulation cascade, fibrinolytic pathway, and kallikrein-kinin pathway, also known as the "contact system". The contact system represents an interface between inflammation, coagulation, and innate immunity,[9-10] and generates bradykinin, the primary pathophysiologic mechanism causing the symptoms of HAE.

More specifically, mutations causing HEA type I cause lower C1-INH blood levels, whereas mutations causing type II give rise to a production of a nonfunctional protein. C1-INH controls the contact system by inhibiting coagulation factor FXIIa and plasma kallikrein. When the inhibitory function of C1-INH is lost, the contact mechanism is activated, leading the formation of higher amounts of kallikrein and to an uncontrolled proteolysis of high molecular weight kininogen and bradykinin formation. An increase in bradykinin release causes an increase in vascular permeability, which in turn increases the amount of fluid that leaks into bodily tissues through blood vessel walls.[11-13] C1-INH-HAE type I and C1-INH-HAE type II patients have periods of swelling due to an extravasation of blood fluid in their bodily tissues. Nonetheless, there is a significant variation in C1-INH levels across HAE patients. A subset of patients exhibit a third form of HAE (nC1-INH-HAE), initially reported by Bork *et al*. and Binkley *et al*. in 2000.[14,15] This variant, distinguished by the absence of mutations in *SERPING1*, has a clinical picture similar to C1-INH-HAE but with normal C1-INH level and activity and affects females more severely than males.[16,17] This variant is linked to mutations in the *F12* gene that is a protein coding gene that encodes coagulation factor XII which circulates in blood as a zymogen. The active factor XII (FXII) participates in the initiation of blood coagulation and in fibrinolysis. It is also an important stimulator of inflammation and is involved in the production of bradykinin. A few mutations in the *F12* gene cause FXII to be produced more actively, with an increase in the production of bradykinin, priming blood vessel walls to become more permeable. Therefore, episodes of swelling in individuals occur, albeit without a C1-INH deficiency. Of the three varieties of HAE, C1-INH-HAE type I accounts for most cases (about 85%), C1-INH-HAE type II accounts for 15% of cases, while nC1-INH-HAE is more uncommon. The disease is inherited in an autosomal dominant manner or arises from a novel mutation.

Mutation in HAE

The location of the mutation in the *SERPING1* gene determines the wide range of clinical symptoms associated with CI-INH deficient HAE. C1-INH-HAE type I mutations are distributed throughout the whole SERPING1 protein.[18,19] C1-INH-HAE type II mutations localize around the protein reactive center loop, with the exception of a mutation in the amino acid residue Lys251, which impacts functionality after protein folding. *SERPING1* exhibits substantial allelic variability; according to the Human Gene Mutation Database (HGMD) and a related database devoted to HAE (HAEdb, hae.enzim.hu), almost 450 distinct variants have been reported.[20] This gene, which contains eight exons and seven introns, is found on chromosome 11 at band location 11q12-q13.1. Its unique promoter lacks a TATA box. This gene has been found to have a number of exonic mutations as well as mutations at intron/exon junctions. These mutations are inherited by autosomal dominant mode. However, sporadic HAE (*de-novo* mutations in the *SERPING1* gene) accounts for about 25% of all C1-INH deficient HAE patients. Approximately 30 to 40% of the variants in the *SERPING1* gene are missense mutations.[21,22] By causing premature stop codon and frame-shift mutations, a variety of nonsense and indel mutations prevent protein synthesis through nonsense-mediated mRNA degradation.[23] Certain non-HAE illness problems have also been linked to single nucleotide polymorphisms (SNPs) in the *SERPING1* gene. A less severe clinical manifestation was only seen in patients with missense mutations that changed a single amino acid.[24] The HAE with normal C1-INH activity is a rarer condition that was first identified at the end of the second millennium[14,15] (Table 1).

Clinical signs of this uncommon form of HAE were found to resemble those of classical types 1 and 2, although no mutation in the *SERPING1* gene was observed. The genetic cause was originally discovered in 2006, when two missense mutations (p.Thr328Lys and p.Thr328Arg) in the exon 9 of the *F12* gene were detected for the first time in six out of twenty German families with nC1-INH-HAE.[22] This protein domain is highly glycosylated and increases the production of activated FXII by plasmin.[32,33] HAE-FXII is inherited as an autosomal dominant trait with incomplete penetrance and is the result of the occurrence of a gain-of-function mutation in the *F12* gene.[25,34] This gene has been shown to harbour additional uncommon pathogenic mutations that are situated between the trypsin-like serine protease domain and the kringle domain, in an area that codes for the proline-rich linker peptide.[35]

Afterwards, the investigation of individuals with nC1-INH-HAE, and their families, who did not carry a *F12* gene mutation allowed the identification of several additional genes associated with nC1-INH-HAE1. In 2018, in individuals with nC1-INH-HAE, a new mutation c.988A > G in the plasminogen (*PLG*) gene was reported,[26,36] in the exon 9, which results in a missense mutation p.Lys330Glu (K330E) in the kringle 3 domain. PLG is the inactive precursor of the plasmin. Plasmin is an enzyme that activates FXII and contributes to the synthesis of bradykinin. Bradykinin is produced at a higher rate as a result of the mutant protein. The p.Lys330Glu variant is transmitted as an autosomal dominant trait with incomplete penetrance, and has been identified in over 14 patients with nC1-INH-HAE from 4 families.[26] In the same year, a missense mutation c.355G > T (p.Ala119Ser) in the angiopoietin-1 gene (*ANGPT1*) was found in affected female

members of a large nC1-INH-HAE family.[27] This mutation interferes with the multimerization of the protein and prevents its ability to bind its receptor on endothelial cells, representing a novel independent mechanism that causes haploinsufficiency-related vascular permeability and angioedema.[37,38] Moreover, Cagini *et al*. discovered additional potentially harmful *ANGPT1* variants (p.Ala8Val; p.Gln370His).[39] In the following years, the investigation of single nuclear kindreds lend to the identification of additional gene variations associated with nC1-INH-HAE. Bork *et al*.,[28] in fact, recognized in a large three-generation German family, a novel variation in the *KNG1,* a gene that encodes for both low- and high-molecular-weight kininogens. The variation (p.Met379Lys) resulted in the substitution of a methionine with lysine and co-segregated with clinical symptoms in relatives with HAE and normal C1-INH levels. In 2020, in an Italian family, three of the four carriers of a rare Myoferlin variant (p.Arg217Ser) were found to be symptomatic. Through a gain of function mechanism, the *MYOF-217S* variant increases the ability of the mutant protein to co-localize to the plasma membrane, together with the Vascular endothelial growth factor (VEGF) receptor-2 (VEGFR-2). The identification of the *MYOF-217S* variant as a cause of HAE suggested a potential role for VEGF-mediated signaling in HAE.[29] Then, in 2021, in a family with nC1- INH-HAE, a variant c.430A > T (p.Thr144Ser) in the heparan sulfate (HS)-glucosamine 3-O-sulfotransferase 6 (*HS3ST6*) was found. The variant allele can lead to an insufficient HS production, suggesting an impairment of interactions on the cell surface leading to angioedema and provide a new mechanism of the disease.[30]

Very recently, in a large Argentinian family, D'Apolito *et al.* identified a rare missense variant in the *DAB2IP* gene (p.Asp239Asn) that has a detrimental effect on the functionality of the DAB2IP protein, leading to the impairment of the endothelial VEGF/VEGFR-2 ligand system (Figure 1).[31]

Targeted next-generation sequencing for the molecular diagnosis of HAE

The application of next-generation sequencing (NGS) technologies, such as genome-wide sequencing and exome sequencing, made possible the identification of additional genes not previously identified as nC1-INH HAE. Apart from its significance in research, NGS is a critical instrument in clinical diagnostics. The usual mutational screening of the coding exons and exon-intron boundaries in the *SERPING1* gene yields no causative mutation in about 5% of C1-INH-HAE patients. The study of *SERPING1* intronic regions is not possible with conventional approaches for genotyping C1-INH-HAE patients. The entire length of *SERPING1* has recently been analyzed using a customized NGS platform, which has allowed for the identification of two pathogenic deep intronic variants: c.-22- 155G > T situated at intron 1 and c.1029 + 384A > G located within the intron 6.[24,40] However, because biochemical C1-INH testing provides a valid and affordable method of testing for C1-INH, and because C1-INH-HAE has significant allelic variability, *SERPING1* genotyping is not advised for this diagnosis. By applying a mutation analysis technique, the diagnosis of nC1-INH HAE can be improved due to the increased understanding of its genetic pathogenesis. To diagnose nC1-INH HAE, genotyping is desirable.[41] As a routine molecular diagnostic biomarker of FXII-HAE, only exon 9 of F12 should be studied because causal *F12* variants to date identified are in the exon 9. In addition to variations in *F12*, pathogenic variants in *PLG, ANGPT1, KNG1, MYOF, HS3ST6 or DAB2IP* may function as diagnostic biomarkers for patients with unexplained angioedema. These variants offer a molecular-level assay that can be used to diagnose HAE in patients with normal C1-INH. Furthermore, it is possible that many more disease genes, including endothelium-associated ones, will need to be investigated in addition to the genes now linked to HAE.[42] The discovery of novel genes and HAE families with nC1-INH will aid in the diagnosis of more patients and the investigation of the pathophysiological mechanisms underlying this condition. A better understanding of mechanisms responsible for the disease will help to identify novel pharmaceutical targets and enhance clinical tools for disease management.[7]

Guidelines for genotyping angioedema patients: the use of genetics in the management of HAE

The question of which genetic testing is appropriate for every individual patient with HAE and how this information may be utilized to guide medical management decisions is becoming increasingly important as the field of HAE genetics expands outside research facilities [42] (Figure 2).

Table 1. HAE genes mutations identified in nC1-INH-HAE.

HAE type	Gene	Nucleotide change	Amino acid change	Variant first described
HAE-FXII	*F12*	c.983 C> Ac.983 C> Gc.971_1018+24 del 72c.892_909 dup	p.T328K. pT328R indel duplication p.298_303	Dewald and Bork (2006)[22] Bork *et al.* (2011)[25]
HAE-PLG	*PLG*	c.988 A>G	p.K330E	Bork *et al.* (2018)[26]
HAE-ANGPT1	*ANGPT1*	c.355 G>T	p.A119S	Bafunno *et al.* (2018)[27]
HAE-KNG1	*KNG1*	c.1136 T>A	p.M379K	Bork *et al.* (2019)[28]
HAE-MYOF	*MYOF*	c.651 G>T	p.R217S	Ariano *et al.* (2020)[29]
HAE-HS3ST6	*HS3ST6*	c.430A>T	p.T144S	Bork *et al.* (2021)[30]
HAE-DAB2IP	*DAB2IP*	c.715 G>A	D239N	d'Apolito *et al.* (2024)[31]

Although sequence variants can be detected more easily thanks to high-throughput sequencing technologies, often it is unknown how these variations will affect protein functionality or gene expression. Furthermore, the concordance between the several methods used to genotype patients with HAE is mainly unclear and the methods themselves are not verified. As a result, the genetic diagnosis of HAE has grown considerably more complicated, and identifying the genetic flaw causing a given case is becoming a more difficult undertaking. Despite C1-INH-HAE's genetic makeup, clinical and biochemical data are typically the only factors used in the diagnosis process. Even though many laboratories can afford it both technically and financially, *SERPING1* gene genetic screening may typically be avoided by measuring C4 concentration and antigenic and functional C1-INH levels, particularly in situations where a family history of angioedema is known.[1] Genetic research, however, might be advantageous in some unique circumstances. The diagnosis of suspected *de novo* cases is one example of this. Furthermore, *SERPING1* screening can be helpful in ruling out the disease in relatives who are asymptomatic as well as in validating a C1-INH-HAE diagnosis when working with HAE patients who do not have a family history.[43] Conversely, only after the corresponding genes have been sequenced can the diagnosis of FXII-HAE, PLG-HAE, ANGPT1-HAE, KNG1-HAE, MYOF-HAE, HS3ST6-HAE or DAB2IP-HAE be made for patients with nC1-INH-HAE. Furthermore, the lack of pathogenic variants in these genes is a prerequisite for the diagnosis of HAE in patients with normal C1-INH levels. Furthermore, segregation studies of novel *SERPING1* variants that cause the disease in several family members should be carried out whenever feasible as they might offer im-

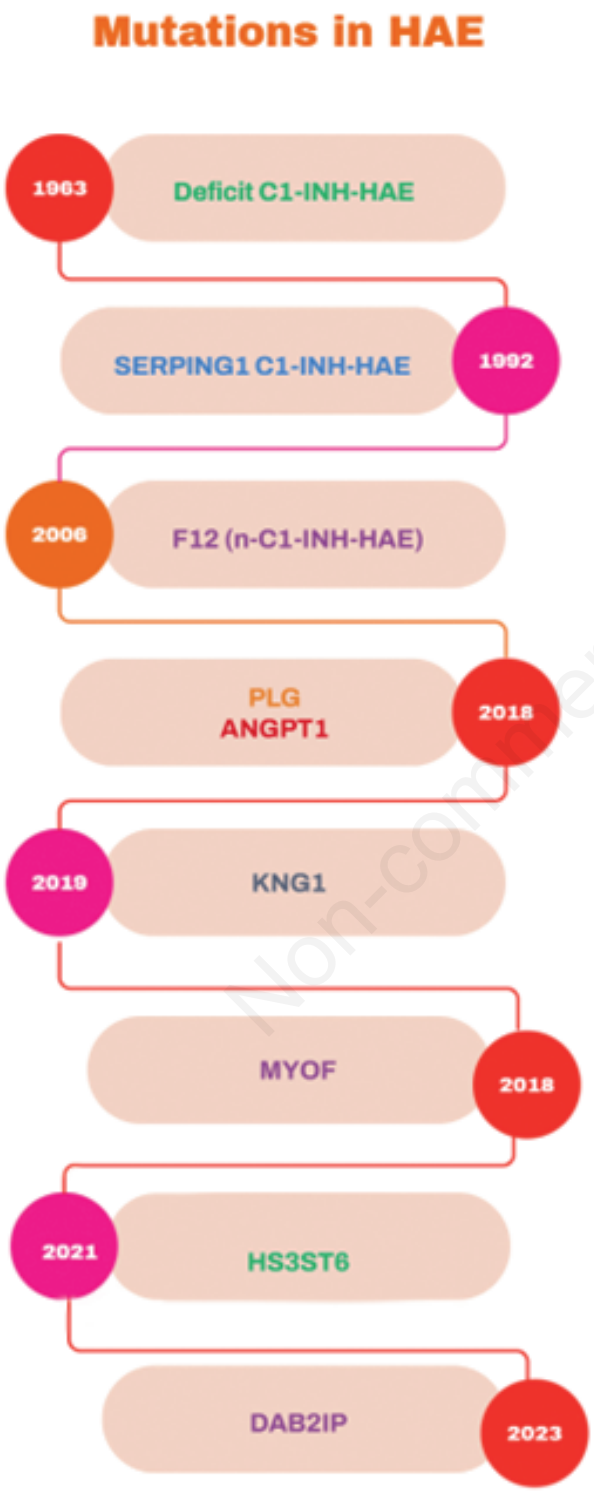

Figure 1. Flowchart timeline of genes discovery.

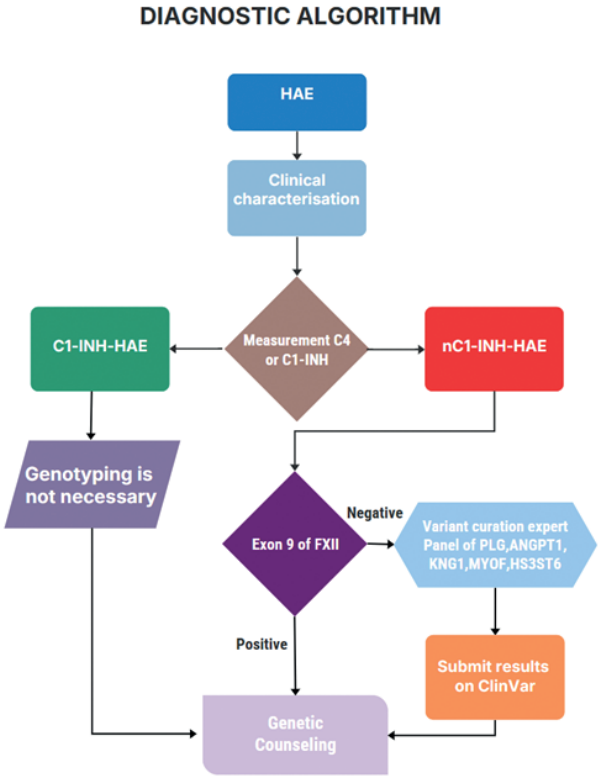

Figure 2. Guidelines for genotyping angioedema patients.

portant proof of their pathogenicity and penetrance. Patients with normal C1-INH levels and functionality, who are suspected of having HAE need to have their nC1-INH-HAE gene variations evaluated. It is advised to carry out genetic counselling in conjunction with professionals who are knowledgeable in human genetics and HAE care. This covers family planning and inheritance mode counselling as well as pedigree analysis. The latter includes information on the prenatal and implantation diagnostics, the danger of interventions and how to prevent them, neonatal screening, and the a priori risk that a planned child will be afflicted by HAE. A clear management plan will be made possible for the mother and baby throughout the pregnancy and birth by close coordination between the genetic and clinical teams. Every nation must include genetic counselling within its legal framework.[42]

Molecular mechanisms regulating vascular endothelial permeability

Vascular permeability regulates the flow of fluids, proteins and immune cells from the blood to tissue and it also contributes to the pathophysiology of many diseases. Increased permeability is a prominent feature of asthma and other inflammatory airway diseases, arthritis, chronic bowel disease, cancer, infections, trauma, ischemic stroke, and many other conditions in which leakage can lead to edema, dysfunction, and morbidity. The endothelial barrier plays a crucial role in regulating vascular permeability. Endothelial barrier function and vascular permeability are regulated by intercellular connections that control the extravasation of plasma and its macromolecular components.[43] Intercellular junctions of endothelial cells are also involved in the formation of structures that develop into sprouts and primitive vascular tubes.[44] The number and arrangement of these connections determine the organ and tissue-specific permeability differences in the vascular system. The barrier is mediated by endothelial cell-cell adhesions CD31/Platelet Endothelial Cell Adhesion Molecule-1 (PECAM-1). Adjacent endothelial cells are connected by protein complexes that are part of gap junctions (GJs), adherens junctions (AJs), tight junctions (TJs) and other adhesion receptors. Changes in vascular permeability are associated with many modulators of endothelial barrier function. Different factors contributing to plasma leakage and edema formation in disease have been identified, and molecular mechanisms leading to changes in vascular permeability have been investigated. VEGFA, angiopoietins (ANGPT1, ANGPT2), histamine and bradykinin have direct effects on endothelial barrier function. Some mediators can induce the formation of smaller or larger gaps between endothelial cells, leading to extravasation.[45]

The activation of endothelial cells by VEGFs has been shown to result in the phosphorylation and disassembly of VE-cadherin, one of the major signaling and structural proteins associated with the AJs. At endothelial junctions, VEGFs and bradykinin increase endothelial permeability by promoting endocytosis of VE-cadherin.[46] This effect is caused by phosphorylation of the intracellular VE-cadherin domain, which is protected by ANGPT1. Bradykinin and VEGFs also induce cytoskeletal rearrangement and contractile response of endothelial cells, leading to disruption of intercellular contacts and increase in permeability.[37]

Furthermore, ANGPT1 contributes to the formation of strong adhesion through the connection between VE-cadherin, β-catenin and cytoskeletal actin. The mutated ANGPT1 caused a change in the cellular distribution of β-catenin, which appeared faint and punctate along the cell-cell boundaries of endothelial cells, suggesting that the ANGPT1 variant is not sufficient to restore endothelial cell-cell contact. Furthermore, stress fiber formation induced by VEGFs and bradykinin was reduced and failed to restore the arrangement of F-actin cytoskeletal elements.[37]

Vasculopathy: a possible link between vascular permeability and HAE

The increase in vascular permeability that leads to angioedema in HAE is modulated by a series of factors that affect the endothelial barrier function. A series of players contributing to plasma leakage and edema formation in the disease have been identified, and the molecular mechanisms causing changes in vascular permeability have been thoroughly investigated.[47] VEGF, histamine and bradykinin directly impact the endothelial barrier function. Certain mediators can prompt the creation of smaller or larger gaps between endothelial cells, leading to extravasation. In particular, VEGF operates through the three structurally similar transmembrane tyrosine kinase receptors, VEGFR1, VEGFR2, and VEGFR3. VEGF is produced by vascular smooth muscle cells. Specifically, VEGFR2, the most prevalent receptor on endothelial cells, is necessary for the increase in vascular permeability induced by VEGFA.[48,49] VEGFs can bind to any of the three receptors, which increases vascular permeability and promotes angiogenesis, among other VEGF effects. By activating an intracellular tyrosine kinase, all receptors function by homo-and hetero-dimerization, which triggers a sequence of downstream events via several shared signaling pathways.[41] Elevated VEGF concentrations have been linked to a number of clinical conditions that are marked by elevated vascular permeability, including sepsis and systemic capillary leak syndrome.[50,51] Lastly, vascular leakage is stimulated by a partial impairment of the process controlling VEGF stimulation on endothelial cells, such as a pathogenic variant causing ANGPT1 or DAB2IP loss of function.[31,37] The reported missense ANGPT1 mutation (p.A119S) caused the inability of the variant protein to form multimers and reduced its ability to bind to the TIE2 receptor, affecting the stability of the endothelial barrier function. This suggests a new, independent mechanism that causes haploinsufficiency, which in turn causes vascular permeability and angioedema.[37] Recently, a new variant within the DAB2IP gene resulted in a pathogenic loss of function of the protein, which affected the stability of the protein and its capability to bind the VEGFR2 and, in turn, to block its activity and the downstream signaling. Furthermore, a pathogenic variant within the MYOF gene was demonstrated to increase, through a gain of function mechanism, the ability of the mutant protein to localize VEGFR-2 to the plasma membrane in response to VEGF stimuli.[29] These findings further support the hypothesis that a dysregulation of the VEGF-mediated signaling has a pivotal role in altered endothelial permeability regulation, thus generating recurrent angioedema attacks (Figure 3).[31]

As a consequence, we now need to expand our understanding of the pathophysiology of HAE beyond the contact system and include molecular pathways that modulate vascular permeability. In this scenario, it could be argued that VEGF, along with potentially other acquired contextual factors, functions as a trigger to locally excite endothelial cells and/or contact systems, hence

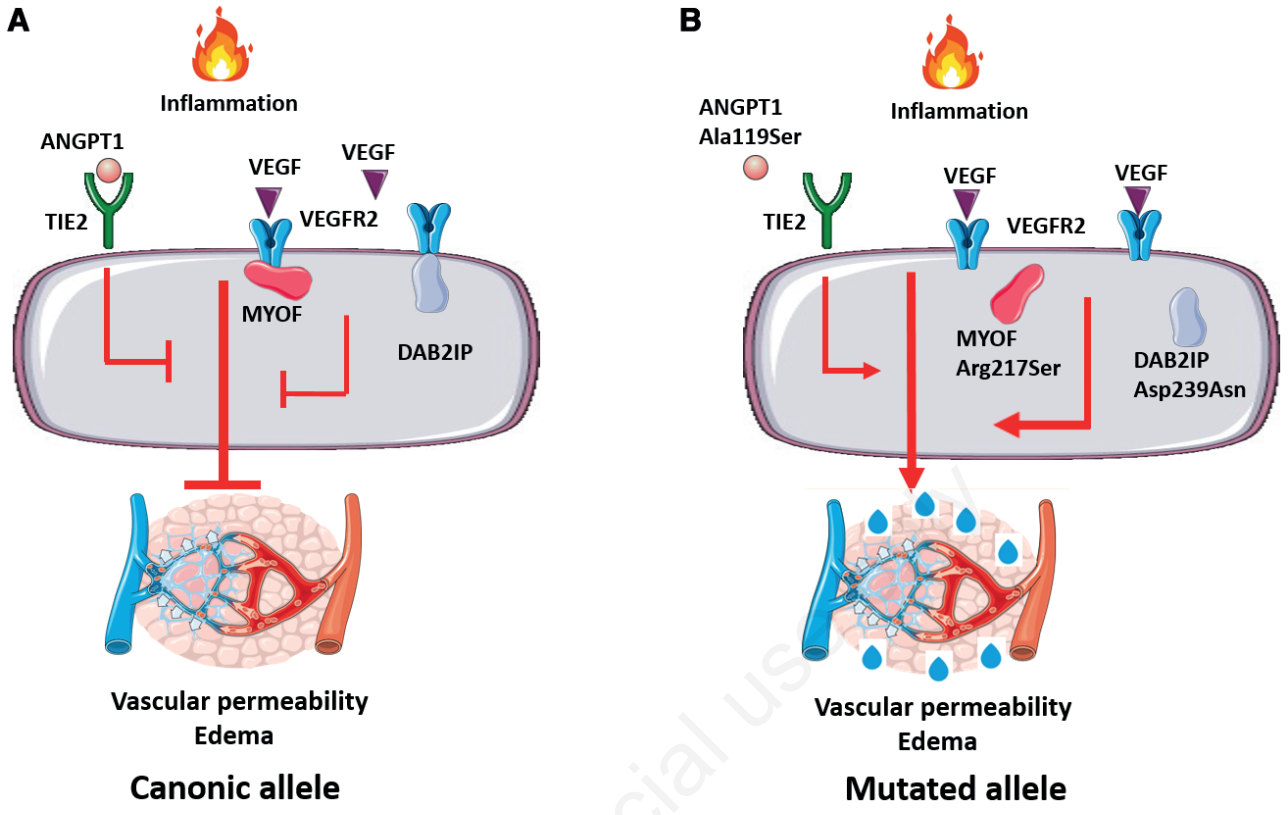

Figure 3. Schematic representation of pathogenic mechanism. Multiple stimuli, as inflammation, bradykinin, histamine, TGFβ induces vascular permeability through different mechanisms. A) Physiologically, ANGPT1 acts as the key regulator of the pathway, by binding to TIE2 domain while MYOF and DAB2IP inhibit to localize VEGFR-2 to the plasma membrane in response to VEGF stimuli. B) The presence of genes variants leads to an impairment of the regulation of vascular permeability and edema condition.

priming the synthesis of bradykinin on surfaces and representing a conditioning environment. While this production is tightly controlled, mostly by C1-INH, in HAE individuals attacks develop because of a higher vascular permeability, usually caused by a genetic reduction in C1-INH plasma levels.[52] These findings offer a tenable mechanism by which patients with pathogenic variants in genes other than SERPING1 gene vascular epithelium become more vulnerable to several mediators that increase permeability, giving rise to uncontrolled bursts of bradykinin.[53] A better understanding of the endothelial cell physiopathology is essential for the elucidation of specific mechanisms that contribute to HAE.[52]

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