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Hereditary Angioedema: Insights into inflammation and allergy

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ABSTRACT

Hereditary Angioedema (HAE) is a rare autosomal recessive bradykinin (BK)-mediated disease characterized by local episodes of non-pitting swelling. Initially considered a complement-mediated disease, novel pathogenic mechanisms uncovered in the last decade have revealed new HAE-associated genes and tight physiological relationships among complement, contact, coagulation, fibrinolysis and inflammation. Uncontrolled production of BK due to inefficient regulation of the plasma contact system, increased activity of contact and coagulation factors or a deficient regulation of BK receptor-triggered intracellular signalling are on the basis of HAE pathology. In this new scenario, HAE can result from different mechanisms that may generate distinct clinical phenotypes of the disease. This review focuses in the recent advances and unsolved challenges in our comprehension of this ever increasingly complex pathology.

1. Introduction

Angioedema (AE) is a rare disease characterised by the local, non-pitting swelling of the submuccosal or subdermic layers.

The pathophysiology of AE is a rapid, transient permeability increase of the capillaries and post-capillary venules in deep skin or mucosae layers due to the local accumulation of inflammatory compounds. It can result from either mast cell degranulation or the release of other mediators mainly bradykinin (Kanani and Betschel, 2018; Kaplan, 2014).

In the former mechanism, AE is usually of rapid development and can be associated with allergic disease and urticaria. In the case of allergic AE, immunoglobulin E (IgE) plays a central role in allergic reactions by cross-linking of the high-affinity receptor FcεRI and inducing the activation and degranulation of blood basophils and tissue-resident mast cells (Kraft and Kinet, 2007). Allergic AE frequently presents with other skin lesions, primarily wheals and immunomodulation effectively restrains edema development. Major preformed mast-cell granule mediators include histamine and tryptase but other *de novo* synthesized molecules like D2 prostaglandins, leukotrienes and cytokines are also implicated (Galli and Tsai, 2012).

Non-allergic AE is far less common than allergic AE (prevalence estimates of 1:50.000 vs 20% of the world population, as estimated by World Allergy Organization) (Mansi et al., 2015) and categorized into several subtypes: pseudoallergic AE (which is commonly a form of mast cell-mediated AE), idiopathic AE, renin-angiotensin-aldosterone system blocker-induced AE, Hereditary AE (HAE) and acquired AE (AAE) (for a review see Radonjic-Hoesli et al., 2018).

HAE and AAE are rare diseases (http://www.orpha.net/) mediated by bradykinin that originate from a loss of regulation on the plasma contact pathway (also known as the plasma kallikrein-kinin system). Currently, HAE is further classified into disease forms associated with decreased levels (type I) or function (type II) of the serpin C1-Inhibitor (C1INH) (**HAE-C1INH**) and those with normal C1INH and C4 levels and function (**HAE-nC1INH**) (Caballero et al., 2011).

Research findings in the last 20 years have given a boost of interest in bradykinin-mediated AE, now blooming in a better comprehension and broadening of the molecular mechanisms involved and in the development of novel and efficient therapeutic options for HAE and AAE patients. This review aims to summarize the recent advances in our understanding of the pathophysiology of bradykinin-mediated AE and to provide a broad perspective of the functional connections and transactivation phenomena occurring among plasma proteolytic pathways and uncovered by HAE research.

2. A brief historical perspective of HAE

Swelling has been recognized as a distinct clinical condition since the ancient times. Dating from as early as the 4th century BC, Hippocrates' Prognosticon first mentions edema as the soft, painless and pitting tumour of organs. In Graeco-Roman times the concept of a tumour (*onkos* in Galen's terminology) included all abnormal swellings of the human body, and was explained on the basis of inflammation. However, the first report of a swelling disorder in medical terms is justly acknowledged to Marcello Donati (1538-1602) by the description of what is now recognized as an allergic AE associated with urticaria in

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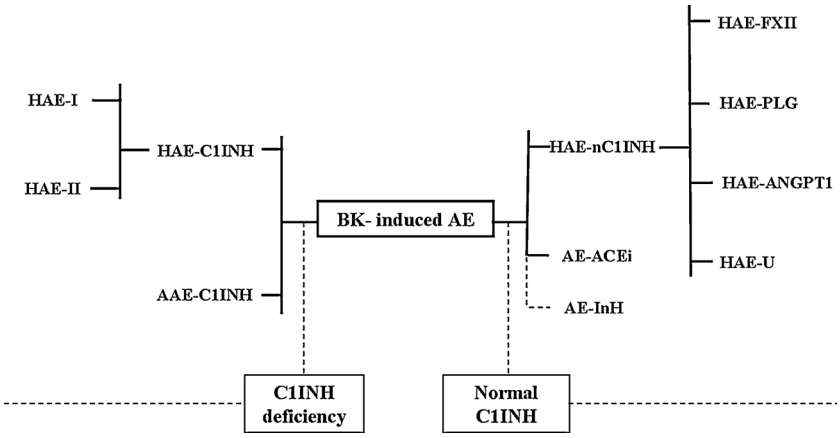

Fig. 1. Classification of BK-mediated AE forms. AE mediated by BK is classified according to the presence or absence of a C1INH deficiency resulting in low C1INH function and C4 levels in serum. C1INH-deficient AE forms can be inherited (C1INH-HAE types I and II) or acquired (AAE-C1INH). AE with normal C1INH can be inherited due to mutations in the *F12* (HAE-FXII), *PLG* (HAE-PLG), *ANGPT1* (HAE-ANGPT1) genes or in other, yet unidentified (U-HAE) loci. It can also present in an acquired form associated to the use of ACEi (AE-ACEi) or be of idiopathic non-histaminergic nature (AE-InH). Abbreviations used: AE, angioedema; BK, Bradykinin; C1-INH, C1 esterase inhibitor; F12, gene encoding the coagulation Factor XII (FXII); PLG, gene encoding Plasminogen (PLG); ANGPT1, gene encoding Angiopoyetin 1 (ANGPT1); ACEi, angiotensin-converting enzyme inhibitors. A dashed line has been used for the classification of AE-InH to indicate only partial evidence for the involvement of BK in its etiology.

his treatise "*De medica historia Mirabilli*".

Later descriptions of patients with swelling are sporadically found during the 18th and 19th centuries by reputed physicians like Franz Anton Mai (1777), Robert James Graves (1843) and John Laws Milton ("Giant urticaria", 1876) (Reshef et al., 2016). But it is the report of a series of cases by the German physician Heinrich Quincke in 1882 which is now considered the first medical description of AE as a distinct clinical entity and which gave rise to the term "Quincke's edema", still used today in many countries (Khan, 2011). Another name for this condition proposed in 1885 by Paul Strübing was "Angioneurotic edema", first drawing attention to the nervous state of the patients as an edema trigger. Soon after Quincke's report, the hereditary nature of AE was finally recognized by William Osler in 1888 while studying a five-generation family with 28 members suffering recurrent attacks of edema (Osler, 2010).

The molecular clues underlying vascular biology and edema development began being uncovered in 1961 with the discovery of the C1 esterase inhibitor by Irwin Lepow and colleagues and the description of the clinical features and differential diagnosis of HAE and allergic AE by Nathaniel Landerman (Lepow and Ross, 1960; Landerman, 1962). Subsequent collaborations between Landerman, Virginia Donaldson and Oscar Ratnoff elucidated the biochemical abnormalities in HAE patients and paved the way for the landmark publications describing the quantitative (HAE type I; Donaldson and Evans, 1963) and qualitative (HAE type II, Rosen et al., 1965) deficiencies of C1INH. During the 1970s and 1980s, the first reports on acquired forms of AE in patients with lymphoproliferative disease were published by Caldwell (Caldwell et al., 1972) and Geha (Geha et al., 1985). Moreover, research during these years deepened the understanding of the role of the contact system in HAE; first, by demonstrating consumption of plasma prekallikrein and high-molecular weight kininogen during HAE crises (Schapira et al., 1983) and also by the Allen Kaplan's group showing that activation of FXIIa by prekallikrein generates a proteolytic fragment (FXIIf or βFXIIa) that activates C1r and prekallikrein (Dunn et al., 1982; Ghebrehiwet et al., 1983), establishing functional links between the complement and contact systems.

However, despite this rapid advance in the knowledge of HAE during the second half of the 20th century, it took almost 30 years of research to univocally identify bradykinin (BK), a small peptide derived from contact-system activation, as the chemical mediator of hyperpermeability in HAE (Nussberger et al., 1998). This in turn allowed the development of novel therapeutic approaches targeting either the proteolytic generation of BK (Ecallantide®) or the binding of BK to its specific receptors on the endothelium (Icatibant®) (Chen and Riedl, 2017).

In 2000, a new variant of HAE (initially referred to as HAE type III or estrogen-related HAE) was simultaneously described by Bork et al and Binkley et al in which AE exhibits the same clinical features as in HAE types I and II, but affects almost exclusively women and is triggered by high oestrogen circulating levels (during oral contraceptive intake, pregnancy, menstruation…) (Bork et al., 2000; Binkley and Davis, 2000). It was soon found that heterozygous mutations in the proline-rich domain of the *F12* gene (encoding FXII) were responsible for the phenotype in a proportion of patients and a gain-of-function effect was postulated (Cichon et al., 2006; Dewald and Bork, 2006). More recently, it has been shown that FXII HAE-causing mutations are associated with defective posttranslational modification of the protease's heavy chain (Björkqvist et al., 2015), this rendering FXII more prone to autoactivation on negatively charged materials, proteolysis by thrombin and FXIa, or enzyme-driven activation by plasmin (de Maat et al., 2016; Ivanov et al., 2019).

3. Classification of BK-induced AE forms

BK-mediated AE can be divided up in two groups: AE due to the deficiency of C1INH, which can be inherited (HAE-C1INH) or acquired (AAE-C1INH), and AE with normal C1INH levels and function (HAE-nC1INH), that can be due to heterozygous mutations in the coagulation FXII, plasminogen or angiopoyetin-1 genes (HAE-FXII, HAE-PLG and HAE-ANGPT1, respectively) or induced by inhibitors of the angiotensin converting enzyme (AE-ACEi). A third form of non-histaminergic AE, in which C1INH levels and function are not affected is Idiopathic non-histaminergic acquired AE (AE-InH). Although experimental evidence for BK involvement in AAE-InH is scarce, it will be briefly commented in this classification for the shake of review thoroughness (Fig. 1).

- **HAE-C1INH** (OMIM#106100) is the most common immune deficiency of the complement system and biochemically characterized by low C1INH levels (Type 1, 85% of HAE-C1INH cases) or function (Type II, 15% of HAE-C1INH cases) and low C4 levels in serum (Caballero et al., 2011).
- **AAE-C1INH** (ORPHA:100056) is considered an ultra rare disease presenting with low C1INH concentrations and/or function, and low C4 levels in the absence of C1INH mutations. A proportion of AAE-C1INH patients distinctively present consumption of C1q. It is Mainly associated with B-cell lymphoproliferative diseases and occasionally with autoimmune, neoplastic, and infectious pathology. Its main diagnostic feature is the detection of neutralizing anti-C1INH autoantibodies in a majority of AAE-C1INH patients (Cicardi and Zanichelli, 2010).
- **HAE-nC1INH** (or **Estrogen-related HAE)** (OMIM#610618) is not associated to decreased C1INH levels or function, and does not present with hypocomplementemia. Despite the association of this disease variant with increased amidolytic activity in plasma (**see pathophysiology, below)**, no standardized laboratory tests are currently available for the diagnosis of Estrogen-related HAE (in

contrast to the low C4 and C1INH levels seen in HAE-C1INH) (Riedl, 2013; Bork, 2013).

A proportion of these patients carry dominant mutations in the F12 gene encoding coagulation FXII (**HAE**-FXII; ORPHA:100054). Several groups have reported low C1INH, levels during acute AE attacks in HAE-F12 patients that return to normality in remission (Vitrat-Hincky et al., 2010; Marcos et al., 2012). Recently, two novel forms of estrogen-related HAE due to mutations in the plasminogen (**HAE**-PLG) and angiopoietin-1 (**HAE**-ANGPT**1**) genes have been described (Bork et al., 2018; Baffuno et al., 2018). The remaining estrogen-related HAE cases with normal C1INH function and without an identified genetic cause are referred to as unknown HAE forms (**HAE**-U).

- **AE-ACEi**. AE may sporadically develop in a minority of patients taking ACEi. There are not specific laboratory tests for AE-ACEi (Cicardi and Zanichelli, 2013). Rather, a clinical diagnosis is made based on the prior usage of ACE-I medications and the disappearance of the symptoms following the discontinuation of medication.
- **AE-InH** is a variant of AE without wheals of unclear etiology defined by the lack of response to antihistamines occurring in patients without a family history of AE not exposed to Acei treatment. Limited evidence exists for the involvement of BK in the pathophisiology of AE-InH (Cugno et al., 2017), which is nevertheless supported by scattered reports on its good response to BK antagonists (Colás et al., 2012; Stahl et al., 2014). However, a more complex etiology is suspected due to additional studies also reporting good responses to the anti-immunoglobulin-E antibody omalizumab (for a review, see Faisant et al., 2017)

4. Clinical features of BK-induced angioedema

4.1. Hereditary and acquired angioedema due to C1INH deficiency (HAE-C1INH and AAE-C1INH)

AE due to C1INH deficiency may be hereditary (HAE-C1INH) or acquired (AAE-C1INH).

HAE-C1INH can present with deficiency or dysfunction of C1INH (HAE-C1INH types I and II, respectively). It is characterized by recurrent episodes of submucosal or subcutaneous marked diffuse edema which is non-pitting, with ill-defined margins and can affect various body locations (face, extremities, genitals, respiratory tract, intestinal and mesenterial structures…) with those involving the skin and extremities being the most common (Caballero et al., 2011). 15% to 30% of patients may develop AE at multiple localizations simultaneously (Hofman et al., 2016). This suggests a systemic component in the onset of attacks, coupled to a locally-increased tissue sensitivity for vasoactive mediators. Attacks typically have a relatively slow onset (hours) and may be preceded by prodromal symptoms including anxiety, asthenia, itching, skin paresthesia, erythema marginatum or muscle pain. When untreated, AE attacks are self-limiting and resolve spontaneously within 48 to 72 hours in most of the cases.

HAE-C1INH presents with no family history of AE in 25% of cases due to *de novo* mutations (Pappalardo et al., 2000). The clinical expression of the disease is extremely variable and has no significant correlation with C1INH levels or function. Although most of the patients first develop symptoms before or around puberty, a proportion of cases can debut at later ages or remain asymptomatic all their lives (Agostoni et al., 2004). Variability in the frequency, severity and location of HAE-C1INH attacks is significant even among patients from the same family. Moreover and despite a considerable consistency in the pattern of AE attacks in some patients, this may not predict the location and extent of subsequent episodes (Farkas et al., 2017).

Abdominal AE attacks mimic acute abdominal diseases such as appendicitis and may cause unnecessary surgical interventions due to improper diagnosis in as much as 30% of undiagnosed patients (Caballero et al., 2011). Episodes can range from slight discomfort to intense abdominal pain progressing to abdominal distension, nausea, vomiting, and constipation (Cicardi et al., 1998). In those patients only presenting gastrointestinal symptoms (21%), HAE recognition is frequently delayed because of misdiagnosis (Talavera et al., 1995).

Upper airways involvement is the most serious clinical manifestation of HAE. Laryngeal, nasal and sinus edema can lead to airway collapse and dead by suffocation. Laryngeal edema occurs at least once in the lifetime in 50% of patients and, if undiagnosed, mortality due to airway obstruction can reach 30% to 40% (Bork and Ressel, 2003).

AAE-C1INH is caused by the presence of autoantibodies targeting and depleting C1INH as a consequence of underlying malignant or autoimmune diseases (Cicardi and Zanichelli). It has the same clinical presentation as HAE-C1INH, although some particular features can help distinguish both pathologies. Unlike HAE-C1INH which usually first manifests during childhood, onset in AAE-C1INH mostly occurs in the forth or fifth decade of life. AAE-C1INH patients have no family history of AE and exhibit poorer responses to C1INH-replacement therapy during acute attacks (Castelli et al., 2007; Cugno et al., 2008). Anti-C1INH autoantibodies have been also detected in HAE-C1INH patients although they are extremely rare and their physiological significance is unclear (Varga et al., 2007; Varga et al., 2011).

4.2. Hereditary angioedema with normal C1INH (HAE-nC1INH)

Hereditary AE without C1INH deficiency (previously named HAE related to Estrogens or HAE type III) is clinically characterized by its dependency on estrogen levels (Bork et al., 2009). It affects almost exclusively women (> 95% of described cases) in whom the edema episodes are triggered or exacerbated in the presence of high levels of endogenous (pregnancy, menstruation) or exogenous (oral contraception, hormone replacement therapy) estrogen levels or Acei treatment, as usually occurs in HAE-C1INH (Bork et al., 2007; Bouillet et al., 2017).

Those affected exhibit the same clinical symptoms described above for C1INH-HAE patients. However, some gene-specific features have been reported. For example, studies of HAE-nC1INH series have found a very significant association of HAE-PLG with swelling of the lips and tongue (reported in 78% of HAE-PLG cases) (Bork et al., 2018; Recke et al., 2019) and a higher frequency of facial AE locations in HAE-F12 (Bork et al., 2007,2009).

4.3. Angioedema induced by angiotensin-converting enzyme inhibitors (AE-ACEi)

The most reported adverse effects related to ACEi treatment are intense cough and AE. ACEi-induced cough can be alarming and difficult to manage at the emergency department but it rapidly resolves upon drug withdrawal (Dicpinigaitis, 2006). AE-ACEi however can be life-threatening regardless of the dose and type of ACEi drug and results from a reduction in bradykinin degradation. A recent meta analysis of 16 randomized trials of ACEIs' safety and efficacy in patients above 65 years documented a 2.8-fold increase in the risk of AE by ACEIs compared with controls (Bavishi et al., 2016).

AE-ACEi usually involves the face, lips, tongue, and the arms, and other cutaneous sites being less commonly involved. Visceral AE-ACEi is rare and may also present with cramping and diarrhea (Byrne et al., 2000). A higher incidence of AE-ACEi has been reported in female, African-American and elderly individuals.

4.4. Idiopatic Non-histaminergic angioedema (AE-InH)

Due to the lack of specific biomarkers, AE-InH is diagnosed by excluding other disorders associated with angioedema without wheals of known etiology and by the failure of antihistamine therapy.

5. Genetics of BK-induced angioedema

5.1. Genetics of HAE-C1INH

Hereditary angioedema due to the deficiency of C1INH (HAE-C1INH; OMIM#) is an autosomal dominant, monogenic disease caused by mutations in the *SERPING1* gene. *SERPING1* is composed of 8 exons and 7 introns spanning 17 kb across the long arm of chromosome 11. Mature, secreted C1INH is a 500 aminoacid protein belonging to the serpin superfamily of protease inhibitors. The C-terminal end of the molecule corresponds to the serpin domain containing the P1-P1' (Arg444-Thgr445) reactive centre site while the 113 N-terminal residues have no homology with any other human protein and are dispensable for protease inhibition (Bos et al., 2002).

HAE type I phenotypes are caused by deletions, insertions or substitutions that may be located across the entire gene and affect one or several *SERPING1* nucleotides hindering C1INH synthesis or secretion. To date, more than 300 HAE type I mutations have been reported usually exhibiting negative dominance over the wild type allele which results in C1INH serum levels ranging from 5 to 30% of normal values. This negative dominance has been attributed both to trans-inhibition phenomena at the RNA level and to an increased catabolic rate of the HAE type I mutations (Zeerleder and Levi, 2016).

HAE type II mutations are missense variants that cluster in or around the reactive center of the molecule and cause a loss of inhibitory function. Owing to its reduced capacity to interact with its target proteases, C1INH from HAE type II patients exhibits a lower catabolic rate resulting in high circulating levels of a dysfunctional protein (Lachmann and Rosen, 1984; Cugno et al., 1990).

As commented above, HAE-C1INH occurs due to *de novo* mutations in a 25% of patients and gross deletions or insertions and genomic rearrangements are found in as much as 15% of cases. Both phenomena are ascribed to the presence of 17 Alu elements distributed across the locus. Alu elements are repetitive sequences of approximately 300 base pairs long that represent the most abundant transposable elements in the human genome. Due to their tandem orientation and repetitive nature, Alu sequences promote non-homologous recombination events that result in genomic rearrangements (Carter et al., 1991).

5.2. Genetics of HAE-nC1INH

HAE-nC1INH is a heterogeneous clinical entity comprising at least 3 distinct pathologies caused by autosomal dominant mutations in specific *loci*.

5.2.1. Genetics of HAE-FXII

A subgroup of patients exhibiting HAE-nC1INH phenotypes (estimated in less than 25% of cases, although with significant population bias) carries heterozygous mutations in the *F12* gene resulting in HAE-FXII (Bork et al., 2015).

FXII or Hageman factor is the zimogen form of the serine protease FXIIa taking part in the plasma contact and coagulation cascades. It is encoded by the F12 gene, composed of 14 exons spanning 12 kb on the long arm of chromosome 5 (5q.35.3), as a single-chain, 615 aminoacid protein. FXII is proteolytically processed to its active, two-chain form FXIIa. It is a multi-domain protein consisting of (in N-ter to C-ter orientation): a type two Fibonecting domain, two Epidermal Growth Factor-like (EGF-like) domains, one type I Fibronectin domain, one Kringle domain, one Proline-rich (PR) domain in the heavy chain and a Peptidase-type catalytic domain in the light chain (Pathak et al., 2015).

A majority of HAE-FXII patients carry the prevalent c.1032C > G (p.T309 K) mutation in the PR domain. It is a founder-effect variant originated in European population around the XI century and frequently associated with HAE-nC1INH in Southern Europe. (Cichon et al., 2006). Pathophysiologically, p.T309 K is considered a gain-of-function mutation that causes overactivation of the plasma contact system and evades C1INH regulation. Although extremely rare, 3 additional HAE-FXII-causing mutations have been described. The missense mutation p.T309R was found in a single European pedigree and affects the same position as the more prevalent p.T309 K variant (Dewald and Bork, 2006). The 72-base pair deletion c.971_1018 + 24del 72, reported in a Turkish-origin family, alters both exonic and intronic positions (Bork et al., 2011). The 18 base-pair duplication c.890-909dup (p.298_303dup) was also found in a single Caucasian patient with HAE-FXII (Kiss et al., 2013). All of the HAE-FXII-causing mutations identified to date are located in the 9th exon of the F12 gene and disrupt the aminoacid sequence of the PR domain, which highlights the important role played by this region of unknown function in FXII activation.

5.2.2. Genetics of HAE-PLG

Plasminogen (PLG) is a zymogen converted to plasmin and angiostatin upon proteolytic activation. PLG is a 92 kDa protein comprised of seven domains: a C-terminal Chymotrypsin-like serine protease domain, 5 Kringle domains and an N-terminal Pan-Apple domain. Plasmin has a molecular weight of 83 kDa. It cleaves fibrin in blood clots and is involved in the proteolytic activation of an array of proteins taking part in inflammation, embryonic development and metastasis. Angiostatin is a 38 kDa peptide that inhibits angiogenesis and tumor metastasis at distant sites by a mechanism involving the plasminogen kringle domains 1 to 4.

In 2018, Bork and colleagues identified the mutation c.988A > G (p.K330E) in the Kringle domain 3 of the *PLG* gene in 14 patients with HAE-nC1INH belonging to 4 families (Bork et al., 2018). The mutation was transmitted as an autosomal dominant trait resulting in a novel type of dysplasminogenemia with pathologic implications (Dewald, 2018).

At the present time, scarce data are still available concerning the prevalence and penetrance of the p.K330E mutation. Although still poorly studied at the genetic and functional levels, its pathologic nature is supported by strict co-segregation of HAE with the mutation in the studied series and, from a mechanistic perspective, by the implication of plasmin in HAE-nC1INH pathology exemplified by (i) the effectiveness of antifibrinolytic agents (for example, tranexamic acid) as long-term prophylactic agents in HAE-C1-INH, HAE-FXII and HAE-PLG patients (Sheffer et al., 1972; Bork et al., 2017; Bork et al., 2018); and (ii) the observation of low levels of PLG activator inhibitors 1 and 2 (PAI-I and PAI-II) in HAE-FXII series, indicating a consumption by PLG activators (possibly tissue PLG activator(tPA) and urokinase PLG activator (uPA) (Joseph et al., 2016).

5.2.3. Genetics of HAE-ANGPT1

Angiopoyetin 1 (ANGPT1) is a secreted protein ligand for 'Tunica Interna Endothelial cell kinase' (TIE2), which is primarily expressed in vascular endothelial cells and a subset of hematopoietic cells. The ANGPT1-TIE2 signalling axis regulates the endothelium barrier function by inhibiting the effects of several permeability factors including Vascular Endothelial Growth Factor (VEGF) and bradykinin (Baffert et al., 2006).

Baffuno et al. have reported the finding of the c.807 G > T (p.A119S) autosomal dominant mutation in the *ANGPT1* gene in a single Italian family previously diagnosed of U-HAE (Baffuno et al., 2018). Patients heterozygous for this mutation have reduced amounts of ANGPT1 in plasma and impaired ability to form ANGPT1 multimers, leading to a reduction in the ability of the mutant protein to bind to the TIE2 receptor due to a mechanism of haploinsufficiency (d'Apolito et al., 2019). In the same study by Baffuno and coworkers, two additional, possibly damaging *ANGPT1* variants in the affected pedigree were also initially considered as the cause of HAE (c.673C > T; p.R225C and c.1478 G > A; p.R494Q) for which functional data are still lacking. Furhtermore, two additional *ANGPT1* variants (p.A8V (c.23C > T) and Q370H (c.1110 G > C)) have been recently reported

in Brazilian families (Cagini et al., 2018), although replication in independent patients cohorts and functional analyses are still lacking.

6. Biochemistry of bradykinin formation and interplay with other enzyme systems

6.1. Kinin formation

Kinins are produced by kallikreins. There are 15 members of the tissue kallikrein family expressed in various tissues. These cleave low-molecular weight kininogen (LK) to release kallidin (lysil-bradykinin; KRPPGFSPFR). However, there is only one plasma kallikrein (PK), encoded by the KLKB1 gene. This enzyme releases bradykinin (RPPGFSPFR) from high-molecular weight kininogen (HK). C1-INH is the most important inhibitor of PK, but it is a very poor inhibitor of tissue kallikreins (Luo and Jiang, 2006). This implicates PK as a major player in the pathogenesis of HAE-C1INH and more or less rules out tissue kallikreins.

6.2. Kinin metabolism

Normally, kinins are short-lived peptide molecules that are subject to enzymatic degradation in tissues and blood. Bradykinin and kallidin are recognized by the kinin B2 receptor (BR2) that is continuously expressed by the vascular endothelium. Removal of the C-terminal Arginine residue from bradykinin or kallidin by carboxypeptidase I (kininase I) lowers its recognition by BR2, and increases its recognition by the kinin B1 receptor (BR1) which is expressed by a variety of cell types at sites of inflammation. Other enzymes can cleave kinins more centrally in their sequence (ACE, DPPIV, Aminopeptidase P, neprilysin; collectively termed kininase II), terminating biological kinin activity (Fig. 2). Lessons from ACEi-AE show us that a tight control over the biological half-life of kinins is essential to prevent pathology.

Although the binding of BK to BR2 has been considered the central pathological event triggering HAE attacks, the involvement of the BR1 receptor and of BK degradation products have also been proposed. HAE is characterized by the relatively slow relapse of the edema episodes. Such prolonged swelling does not conform to the rapid desensitization observed experimentally with BR2. Zuraw and Christiansen recently proposed that BR1, the inducible BK receptor, may play a role by sustaining the attacks. B1R expression and signalling significantly increase upon binding of the BK metabolite des-Arg^9-BK (Zuraw and Christiansen, 2016). This is a relatively new research field in HAE that needs further experimental validation.

6.3. Links to other enzyme systems

6.3.1. Coagulation and thrombosis

Plasma kallikrein (PK) is part of the plasma contact system, which is mostly known for its role in diagnostic *in vitro* coagulation assays. In these assays, citrated plasma is first exposed to silicon-rich clay-derived minerals, which cause FXII to activate (FXIIa). Subsequently, calcium and phospholipid vesicles are added to the plasma and coagulation times are determined. Activated FXIIa has two direct targets to activate through cleavage: PK and Factor XI (FXI). Once PK is activated (PKa), it reciprocally assists in FXII activation, thereby accelerating contact activation (Asmis et al., 2002). Once FXI activity is triggered, the coagulation system becomes active in a calcium-dependent manner, ultimately followed by thrombin and fibrin formation (Fig. 2) (Naito and Fujikawa, 1991).

It is puzzling that FXII, PK or HK are not needed for physiological hemostasis; human subjects as well as knockout mice that do not express these proteins appear perfectly healthy and without bleeding problems. However, *in vivo* studies show that the contact system contributes to thrombosis – the formation of blood clots that obstruct the vasculature. Targeting of contact factors with antibodies or antisense oligonucleotides in mice and primates holds the promise as a safe antithrombotic strategy (Cheng et al., 2010; Revenko et al., 2011; Matafonov et al., 2014). On a critical note, one might ask whether these experimental models for thrombosis accurately reflect the human condition: HAE-C1INH and HAE-FXII patients do not appear to have an increased thrombotic risk. In other words, pathological hyperactivity of the contact system does not appear to have thrombotic consequences on a clinical level. However, on a serological level, there is evidence for a consumptive coagulation reaction: D-dimer levels are elevated in HAE-C1INH patients during periods of clinical remission and rise further during acute swelling attacks. The same is true for thrombin-antithrombin complexes (Nielsen et al., 1996), as well as prothrombin fragment F1 + 2 (Cugno et al., 2009).

6.3.2. Plasminogen activation

Plasminogen activation has the breakdown of fibrin polymers in blood clots as its main purpose. Hereto, endothelial cell-derived tissue plasminogen activator binds to fibrin polymers and develops enzymatic activity. This mechanism is not dissimilar to contact activation, which may relate to the homology between tPA and FXII. However, in this case, plasminogen is the direct target of active tPA. It was already described decades ago that plasmin can cleave and activate FXII in solution (Kaplan and Austen, 1971), but initially without clinical implications. Later, it was demonstrated that pharmacological plasminogen activation for myocardial infarction leads to FXII activation *in vivo* (Ewald and Eisenberg, 1995). This phenomenon may help to explain how tissue (brain) oedema develops after thrombolytic stroke therapy (Marcos-contreras et al., 2016; Simão et al., 2017.) In addition, angioedema is a rare side-effect of thrombolytic therapy that can be managed with B2R antagonists (Brown et al., 2018; Cheong et al., 2018). We recently found that mutations in FXII that cause HAE amplify the activation reaction by plasmin (de Maat et al., 2016; de Maat et al., 2019). Around the same time, others have found evidence for a deregulated plasminogen activation system through lowered PAI-2 plasma levels (Joseph et al., 2016).

Another group found with a microarray gene expression analysis on RNA that circulating peripheral blood mononuclear cells express higher urokinase plasminogen activator (uPAR) levels. This receptor is involved in plasminogen activation on the surface of (activated) endothelial cells (Castellano et al., 2018). Finally, genetic studies in HAE patients with normal C1-INH activity have taught us that a single point mutation in the plasminogen gene is associated with disease in patient families across the world (Germenis et al., 2018; Yakushiji et al., 2018; Belbézier et al., 2018; Dewald, 2018). The underlying biochemical explanation for this gain of function is currently unknown, but naturally of high interest. It might fit with earlier biochemical studies (Christen et al., 2010) on plasminogen's kringle 3 domain: this domain naturally does not bind lysine residues (which target fibrin for destruction) unless a specific residue (K57; corresponds to K330 in full-length plasminogen) is mutated. On a biochemical level, the human plasminogen mutation that causes HAE, appears to induce this type of change.

6.3.3. Complement activation

There are several links between the complement system and the contact system. For example, the receptor for C1q, C1qR, is involved in the recruitment of contact factors to endothelial cells (Joseph et al., 1996). On an enzymatic level, it has been described that FXIIf (also known as β-FXIIa, a truncated activation product of FXII) activates the complement system in serum through C1 activation in a plasmin-independent manner (Ghebrehiwet et al., 1981). More recently, it was found that PKa acts on C3 in a similar manner (Irmscher et al., 2018). Finally, we should overlook that C1-INH is important for control over both contact system- and complement enzymes. However, despite the use of C4 consumption as a biomarker for HAE (Kaplan and Maas, 2017) and evidence for complement activation during HAE attacks (Nielsen et al., 1996), it appears that it has a limited contribution to the

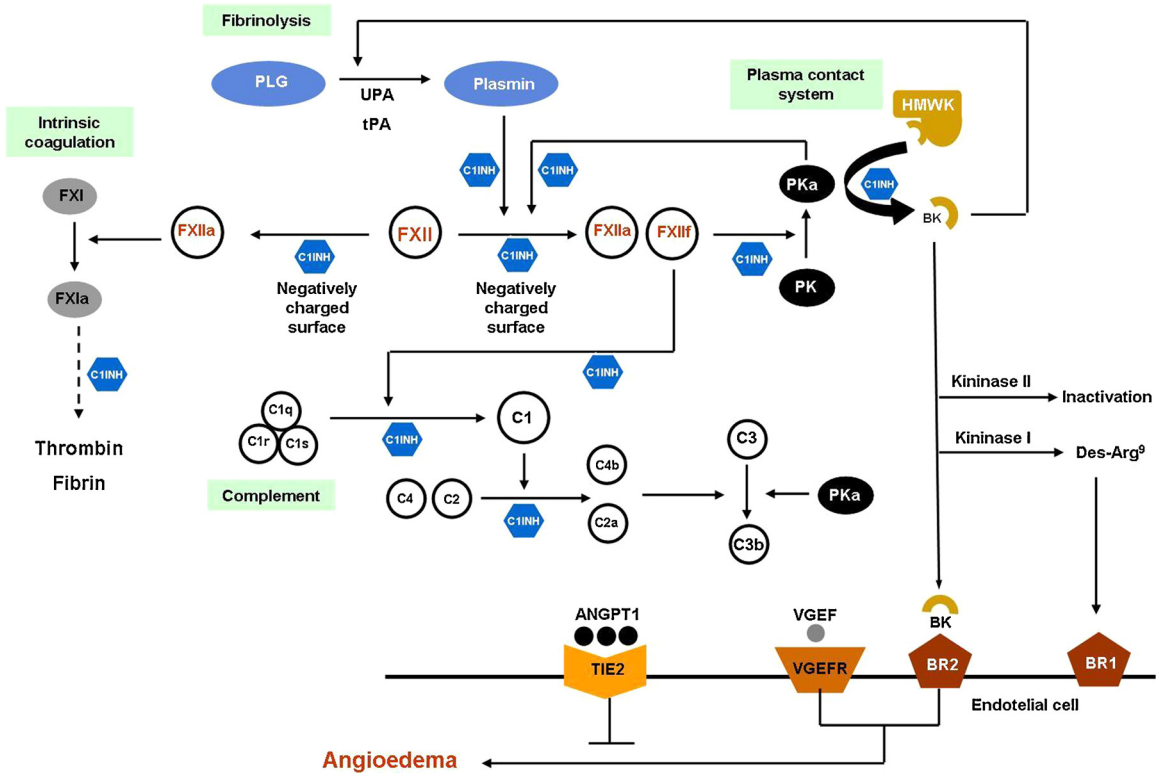

Fig. 2. Enzymatic pathways involved in HAE. The activation of the plasma contact pathway is the hallmark pathological event common to all BK-mediated AE forms. It starts with FXII proenzyme autoactivation taking place upon contact with negatively charged surfaces and the release of the active protease FXIIa, which can activate PK to PKa. PKa in turn activates more FXII molecules and cleaves HMWK to release BK, which then binds BR2. BK is a short-lived nonapeptide that can be inactivated by plasmatic proteases (collectively referred to as Kininase II) or modified by Kininase I to render the metabolite des-Arg^{9}-BK preferentially binding BR1. Edema development upon BR2 binding requires coestimulation of VEGFR and is negatively regulated by the ANGPT1-Tie2 axis. FXIIf and PKa induce the activation of the classical pathway of complement, by respectively activating the C1 and C3 components. Finally, BK can induce fibrinolysis transactivation by promoting plasmin release in UPA or tPA-dependent manners. Released plasmin in turn activates FXII to FXIIa. Reactions controlled by C1INH are indicated. Abbreviations used: BK, Bradykinin; AE, angioedema; C1-INH, C1 esterase inhibitor; FXII, coagulation Factor XII ; FXIIa, activated coagulation Factor XII; FXIIf, betha-FXIIa; PK, Plasma Kallikrein; PKa, activated Plasma Kallikrein; HMWK, High Molecular Weight Kininogen; BR1/BR2, Bradykinin Receptors 1 and 2; VEGFR, Vascular Endothelial Growth Factor; UPA, Urokinase-tipe Plasminogen Activator; tPA, Tissue Plasminogen Activator.

pathogenesis of HAE. This is amongst others based on the unique clinical observation in a patient family: carriers with a C1-INH mutation that selectively renders it unable to block complement factors (i.e. it still blocks contact system enzymes) do not develop angioedema (Zahedi et al., 1995)

6.3.4. *The ANGPT1-TIE2 axis*

The 'Tunica Interna Endothelial cell kinase 2' (TIE2) receptor is an important regulator of vascular barrier function in health and in disease whose expression is increased at sites of inflammation and vascular remodelling (Woo et al., 2011). In angiogenesis, TIE2 complements the function of the major mitogenic factor VEGF. TIE2 binds ANGPT1 and ANGPT2 molecules produced by peri-endothelial cells and platelets with opposing effects: while ANGPT1 stabilizes the endothelial barrier, ANGPT2 counteracts vascular signalling exerted by ANGPT1 and may induce plasma leakage and endothelial cell apoptosis (Harfouche et al., 2002). Experimental evidence in humans and animal models has shown that barrier defense mediated by TIE2 upon ANGPT1 binding is directed by a signalling cascade that triggers cell-spreading, characterized by a cortical distribution of fibrillar actin and increased junctional accumulation of VE-cadherin (Milam and Parikh, 2015; Witzenbichler et al., 2005).

ANGPT1 signalling through TIE2 requires a two-step multimerization process of ANGPT1 molecules: a coiled-coil domain first enables oligomerization and a unique N-terminal superclustering domain then promotes high-order multimerization, which is critical for the interaction of the C-terminal fibrinogen-like domain of ANGPT1 to bind the receptor (Huang and Kovac, 2003; Milam and Parikh, 2015). The p.A119S mutation described by Bafunno and colleagues in HAE patients is located in the first portion of the coiled-coil domain. The authors demonstrated that the mutation did not significantly affect ANGPT1 protein levels but renders the mutant protein defective in high-order multimerization which in turn prevents effective interaction with TIE2 (Bafunno et al., 2018).

Pretreatment of endothelial monolayers with ANGPT1 attenuates the permeability-inducing effects of BK (Pizurki et al., 2003), which strongly indicates that this new HAE type is also BK-mediated. The unexpected involvement of the ANGPT1-TIE2 axis in HAE is important as it sheds light on an endothelial barrier modulator largely independent of bradykinin regulation or catabolism that can cause HAE under pathologic conditions. However, larger series of patients and additional systematic studies are still needed to deepen our knowledge about the genetic, clinical and physiological features of HAE-ANGPT1.

7. Conclusions

The last twenty years have supposed a sweeping change in our understanding of HAE. Initially regarded as a purely complement-mediated disease characterized by the quantitative or functional deficiency of C1INH, advances made in basic and clinical research have broadened both the pathological basis and therapeutic approach to HAE. First, the recognition of the plasma contact system instead of the complement pathway as the main mediator of the edema episodes in HAE changed the focus of research toward FXII, PK and BK as the major

players involved. Subsequently, the identification of non-hypocomplementemic HAE forms with normal C1INH in which the development of edema shows a strong dependence on estrogen levels and the availability of high throughput sequencing techniques prompted the discovery of novel genetic causes of HAE. The particular roles played by FXII, PLG and ANGPT1 in HAE and the precise implication of BK in their physiopathology are still the focus of active research. However, it is now clear that the loss of endothelial barrier function depicted by HAE attacks originates from a loss of homeostatic imbalance which may involve different extra- and intracellular pathways. These recent findings place HAE as a subject of increasing complexity that will possibly provide valuable information for our better understanding of complement, contact, coagulation, fibrinolysis and inflammation.

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