

Editorial

Hereditary Kinin-Mediated Angioedema: Current Challenges

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Editorial

Firstly described in 1882 by Heinrich Quincke, angioedema was regarded for more than one century as a rare disease [1]. Subsequently, it was established that the hereditary form of the disease (Hereditary Angioedema, HAE) is caused by a deficiency of C1-Inhibitor (C1-Inh) [2] due to alterations in the encoding *SERPING1* gene [3] and Bradykinin (BK) was recognized as the principal mediator of HAE symptoms [4]. Over the past decade, however, impressive research advances uncovered an astonishing complexity of the disease. As a result, nowadays, kinin-mediated angioedema is considered as adverse family of disorders, whose the only common characteristics is an unpredictable clinical expression by spontaneous, recurrent, self-limiting but potentially life-threatening attacks of localized edema of subcutaneous and submucosal tissues. Thereafter, a series of challenging pathophysiological and genetic aspects of the disease that remain to be deciphered, are continuously revealed.

Angioedema attacks result from an increased vasopermeability that is induced by the generation of BK through a local process precipitated by systemic contact system activation. Convincing evidence about the systemic kinin formation is that swellings during a given angioedema attack can occur at multiple sites, as well as that inhibitors able to control kallikrein activity reduce vasopermeability and attack severity [5].

C1-Inh is the major control of contact phase proteases, targeting kallikrein and FXIIa. It plays a role in regulating its systemic, fluid-phase activation, and in preventing dissemination of contact activation process. Therefore, C1-Inh deficiency is associated with uncontrolled contact phase activation and, subsequently, with generation of vasoactive peptides, BK and its active metabolite *desArg⁹-BK* after being processed by carboxypeptidases N/M. Another kinin, called kallidin (*Lys-BK*), can be produced from low molecular weight kininogen. *Lys-BK* is transformed by carboxypeptidases into

desArg⁹-Lys-BK. These vasoactive peptides, BK, *Lys-BK* and their metabolites *desArg⁹BK*, and *desArg⁹-Lys-BK* interact with G-coupled protein receptors B2R and B1R. Local angioedema attacks depend on the local receptor expression, in particular B1R in inflammatory conditions and its activation by agonists *desArg⁹-BK* and *desArg⁹-Lys-BK*. The potency of these agonists to stimulate B1R is not reflected by affinity. B1R agonists are with sufficient concentration and with long half-life enough to stimulate B1R [6]. Besides, the agonistic activity of *desArg⁹-BK* for B1R is enhanced by CPM [7].

The main enzyme for *desArg⁹-BK* catabolism is Aminopeptidase P (APP); its activity in C1-Inh deficient patients' plasma, inversely correlate with disease severity, supporting a role for *desArg⁹-BK* in HAE attacks [8]. On the other hand, in FXII-HAE patients, the severity inversely correlate with ACE and CPN activity rather than with APP levels [9].

As far as the genetics of angioedema is considered [10], the main discovery made at the turn of the century is that C1-Inh deficiency is not the only cause of HAE. Cases of inherited angioedema with normal plasma levels of fully functional C1-Inh and without causal mutations at the *SERPING1* locus (nC1-Inh-HAE) are recognized increasingly often, especially amongst patients suffering from estrogen-associated HAE. Nearly a tenth of nC1-Inh-HAE cases could be attributed to gain-of-function mutations in the gene encoding the coagulation Factor XII (*F12*) [11]. Interestingly and on the contrary to the uniform C1-Inh-HAE epidemiology around the world, FXII-HAE seems to be prevalent in certain areas, a fact indicating that the responsible *F12* mutations may represent a founder effect. In any case, this discovery signifies that the genetic basis of HAE is far from being completely understood. Since isolated or combined deficiencies in enzymes involved in kinin degradation (carboxypeptidase N, angiotensin-I converting enzyme, APP) have been detected in various forms of kinin-mediated angioedema [12], it is not improbable that in the future, causative alterations in genes other than *SERPING1* and *F12*, will be detected.

Moreover, accumulating evidence indicates that functional mutations in genes encoding proteins involved in kinin metabolism and/or function are associated with the severity of C1-Inh-HAE or with the emergence of acquired angioedema. Should these findings will be confirmed, they will explain, at least partially, the enormous clinical heterogeneity of the disease observed even among members of the same family sharing the same *SERPING1* causative mutation. Generally, the better understanding of these associations will help to develop strategies to deal with their implications for the individual patient.

Besides, in about 5% of C1-Inh-HAE cases, no mutation can be detected in the coding region of *SERPING1*. But the fact that almost all suffering heterozygotes present with plasma C1-Inh concentration

lower than the expected 50% (approximately 10-30%), has not as yet reached a satisfactory explanation on the basis of the post-translational characteristics and effects of the truncated C1-Inh [10]. These observations indicate that causative defects modifying C1-Inh expression may be located in an intronic or an untranslated region of the *SERPING1* gene. Accordingly, C1-Inh expression may be modified by epigenetic alterations, the effect of which becomes more probable considering that the disease may follow a variable course in the different life periods of the same patient. Finally, a recent finding that the proportion of the various types of disease-related *SERPING1* alterations is different between distinct geographical regions [13] indicates the possible implication of environmental factors either in the mutagenesis or in the epigenetic regulation of the gene.

Appropriate genome-wide studies are also expected to elucidate many others of the unmet problems of angioedema. For example, the localization of high-affinity estrogen response elements in genes encoding proteins involved in HAE pathogenesis would shed light on the gender hormone-mediated effect that remains one of the most complex features of HAE. Genomic approaches would also explain the relationship between the acquired C1-Inh deficiency, lymphoproliferative disorders, and autoimmunity and might shed light on angioedema phenotypes, as well as on their complex interplay with lymphomagenesis [14].

An accurate biological diagnostic for angioedema condition is difficult; the first line of usual laboratory diagnostic is C1-Inh function [15]. The biological profile of HAE patients is changing in the course of the clinical phenotype. HAE patients have increased kallikrein-dependent enzymatic activity in plasma during attacks [16], which indicates a kinin production process. For patients who have a sustained kinin catabolism, the attacks are less recurrent, and patients develop less severity as mentioned above. Besides, groups of patients present with a compromised kinin catabolism capacity as causative factor [12].

Any attempt towards the clarification of the above issues of angioedema is directly and closely interrelated with its many unresolved diagnostic, prognostic, preventive aspects, and finally, with the treatment and the healthcare of patients. The main priorities behind these unresolved aspects are:

(a) The development of self-monitoring methods that will allow an objective follow-up of the clinical course and valid measurements of the disease severity, explicitly or implicitly through appropriate technologies. Using mHealth apps, personal health devices, sensors/IoT (Internet of Things) artefacts and standardized evidence-based questionnaires, appropriate disease-specific data capturing tools can be provided and the quantified-self (phenome), a key ingredient for constructing robust Electronic Health Records, can become achievable [17].

(b) The identification of reliable genetic, epigenetic and/or biochemical biomarkers is needed for special diagnoses (e.g. nC1-Inh-HAE or idiopathic non histaminergic acquired angioedema), but it is more pressing in regard to the long-term prognosis and the response to the treatment as well as with the prediction of angioedema attacks. Despite the many efforts made separately by various groups [15,16,18], no validated single biomarker is available as yet, whilst

the possibility of multiple or combined biomarkers has been never examined.

In conclusion, the above challenges point all to one question: – How possible is for the traditional translational research approach to cope with the emerging enormous complexity of angioedema and to formulate medical practices tailored to an individual patient based on the intrinsic biology in addition to clinical signs and symptoms? The everyday arising puzzling genetic and pathophysiological questions compounded by the intractable angioedema heterogeneity indicate that the current translational research model has reached an inflexion point.

This is reflected in the persistent attempts recently made towards a classification of angioedema [12,19-21]. Undoubtedly, angioedema taxonomy is expected to have important consequences for understanding and managing the disease. However, all proposed classifications are schematic, inflexible and narrow in that they do not dispose a rationale for building a continuum of research and clinical care. The reason is that they have been based on observations of symptoms and signs, and variable molecular knowledge of disease mechanisms but not on accurate disease descriptors simply because such descriptors are not yet available. Thus, high-throughput (omics) approaches are firstly required for the identification of such descriptors (genes, their regulators, and their products) for angioedema. Through network-based analyses of such omics data and module approaches, a systems level and a molecular understanding of disease mechanisms would be obtained [22].

In other words, if angioedema research and healthcare aim to find the right drug, for the right patient, at the right time, every time, their main facing challenge is to switch into a Precision Medicine approach. Such an approach of angioedema is also expected to facilitate the overcoming of limitations that exist in developing Precision Medicine models for more common diseases.

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