ADVANCES IN UNDERSTANDING OF THE PATHOPHYSIOLOGY OF HEREDITARY ANGIOEDEMA (HAE)
Hereditary Angioedema (HAE) – Background

- Patients suffer episodic swelling, without urticaria
  - face, oropharynx, GI system, genitalia, extremities
- Autosomal dom. ~ 1:50,000, no strong race bias
- Type I: *Serpina1* gene mutations cause loss of expression of C1 esterase inhibitor (C1-INH)
- Type II: *Serpina1* mutations lead to non-functional C1-INH
- Type III: HAE with normal C1-INH – over-active FXII?
- In all types, the potent vasodilator bradykinin (BK), is produced in excess, causing vascular leakage and edema
The contact system is pivotal in HAE pathophysiology

- Insufficient C1-INH or enhanced enzymatic activity leads to pathological bradykinin generation
# HAE therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute therapies</strong></td>
<td></td>
</tr>
<tr>
<td>C1-INH IV (Plasma &amp; recomb.)</td>
<td>C1-INH replacement</td>
</tr>
<tr>
<td>Ecallantide (small protein)</td>
<td>Kallikrein antagonist</td>
</tr>
<tr>
<td>Icatabant (small molecule)</td>
<td>BK2R antagonist</td>
</tr>
<tr>
<td><strong>Prophylactic therapies</strong></td>
<td></td>
</tr>
<tr>
<td>C1-INH IV</td>
<td>C1-INH replacement</td>
</tr>
<tr>
<td>Attenuated androgens e.g. Danazol</td>
<td>Enhances C1-INH secretion</td>
</tr>
<tr>
<td>Lysine analogues e.g. Tranexamic acid</td>
<td>Anti-fibrinolytic, inhibits plasmin</td>
</tr>
<tr>
<td><strong>Therapies in development</strong></td>
<td></td>
</tr>
<tr>
<td>C1-INH SC (plasma, ↑conc.)</td>
<td>C1-INH replacement</td>
</tr>
<tr>
<td>Monoclonal antibody – anti-kallikrein</td>
<td>Blocks enzymatic kallikrein activity</td>
</tr>
<tr>
<td>Small molecule</td>
<td>Kallikrein antagonist (oral)</td>
</tr>
<tr>
<td>Anti-sense nucleic acid</td>
<td>Prekallikrein knockdown</td>
</tr>
<tr>
<td>Monoclonal antibody – anti-FXIIa</td>
<td>Blocks enzymatic FXIIa activity</td>
</tr>
</tbody>
</table>
Disease Variability in HAE

- While C1-INH levels are pivotal, other factors contribute to disease variation
  - C1-INH (>300 variants) - differences b/w complement & kallikrein regulation activity
  - BK catabolism - multiple enzymes e.g. ACE, APP, NEP
  - Contributions of fibrinolytic system
  - High variability in FXII concentration levels (60-140%)
  - Variability in endothelial susceptibility to leakage

HAE disease state

- Frequency of attack
- Symptom severity
- Locale of swelling
- Symptom duration
- Therapy response
Triggers for HAE attacks

• Relationship b/w biochemical and HAE triggers poorly understood
  – HAE triggers: physical trauma, surgery, dental extraction, stress, infection, menstruation, underlying pathologies

• Multiple triggers of contact system activation proposed
  – FXII activation through contact at various physiological surfaces
    • eg. collagen, DNA, misfolded proteins, polyphosphates
  – Plasmin activation of FXII
  – Prolyl-carboxypeptidase (PRCP) activation of prekallikrein\textsuperscript{a}
  – HSP90 activation of prekallikrein\textsuperscript{b}

• In health, C1-INH prevents any trigger from leading to edema

\textsuperscript{a} Shariat-Madar Z, Mahdi F, Schmaier AH 2002 J Biol Chem 277;
\textsuperscript{b} Joseph, Tholanikunnel, Kaplan, 2002 PNAS 99
Plasminogen activation in HAE attacks

• Such activation may influence propagation of & precede HAE attacks
  – Tranexamic acid has prophylactic benefit in some patients
  – D-dimers elevated in patient attack samples, and often remission samples
  – tPA can be released from activated endothelial cells

• Activation models proposed, either kallikrein- or FXII-mediated\(^a\)
• Both require FXII-driven amplification for pathological BK formation
• Plasminogen or FXII activation drives the FXII model
• PRCP, HSP90 or trace plasma kallikrein drives the kallikrein model

\(^a\) de Maat, de Groot and Maas, 2014, Semin Thromb Hemost
HAE with normal C1-INH (HAE-nC1-INH; Type III)

- Patients suffer HAE attacks clinical similarities to type I and II
  - First described in 2000 by Bork et al\(^a\)
- Prevalence – several hundred families, but maybe many more
- Mostly females, estrogen linkage - FXII gene estrogen response element
- Significant proportion of these patients have FXII mutation at aa309
  - mutation introduces new plasmin cleavage sites\(^b\)
  - mutation leads to defective FXII glycosylation\(^c\) – ↑FXII activity
- PAI-2 deficiency\(^d\) in type III patients with and without FXII mutations
  - likely due to excess consumption
- FXII hyper-activity appears to overcome normal C1-INH regulation
  - fibrinolytic contribution; basis in patients without FXII mutation unclear

Role for BK1R? – local or systemic activation

- BK engagement with constitutive BK2R believed to drive localised edema episodes
- BK1R up-regulated in inflammation – role for systemic activation?
- Supporting observations:
  - Episodes often involve swelling at multiple locales
  - Drops in blood pressure not observed
  - Modest level systemic C1-INH therapy alleviates symptoms
  - Prodromal symptoms suggest systemic activation
- Model proposed by Zonne et al\(^a\) where:
  - Initial BK activation leads to BKR2 desensitisation
  - BK-mediated inflammation leads to BK1R up-regulation
  - Angioedema occurs at sites of endothelial BK1R expression

FXII is pivotal in HAE: C1-INH is its main regulator

- FXII inhibition as a therapeutic strategy:
  - many contact system triggers but FXII key for pathological amplification
  - Hageman’s patients have no enhanced thrombosis risk
  - FXII >90% regulated by C1-INH; kallikrein regulated ~ 50/50 C1-INH α2-M
  - Treatment with a FXII inhibitor could restore regulation of deficient C1-INH

FXIIa-med. Kall activity in 80% normal v HAE plasma with CSL312 inhibition

FXII antibody "normalises" kallikrein-kinin pathway of HAE plasma ex vivo

FXII inhibition prevents BK generation (LC-MS/MS assay)
Anti-FXIIa mAb, inhibits ACEi-induced angioedema

C1-INH -/- mice → i.p. mAb → i.v ACEi (Captopril) 2.5 mg/kg → i.v. Evan's blue → Dye extraction

Colon

ACEI

Basal

3F7/ACEI

BM4/ACEI

FXII antagonist mAb: 3F7 – CSL312 parent mAb

Graphs showing OD @ 620 nm for different treatments.
Pathways relevant to HAE pathophysiology

- The contact system, with FXII at its apex is pivotal in HAE
  - Dysregulation of this system due to insufficient C1-INH or enhanced enzymatic activity leads to pathological bradykinin generation

![Pathway diagram](image-url)
SUMMARY

• HAE attacks are mediated by bradykinin
• Multiple pathways intersect the contact system
  – affecting disease variability and therapeutic response
• Mechanism underlying HAE triggers poorly understood
• Important pathophysiological role of fibrinolytic system
• HAE Type III may result from hyperactivity of FXII,
  – Disturbing the balance of contact activation and regulation
• FXIIa amplifies pathological bradykinin production – novel HAE target
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