Pathophysiology of Angioedema

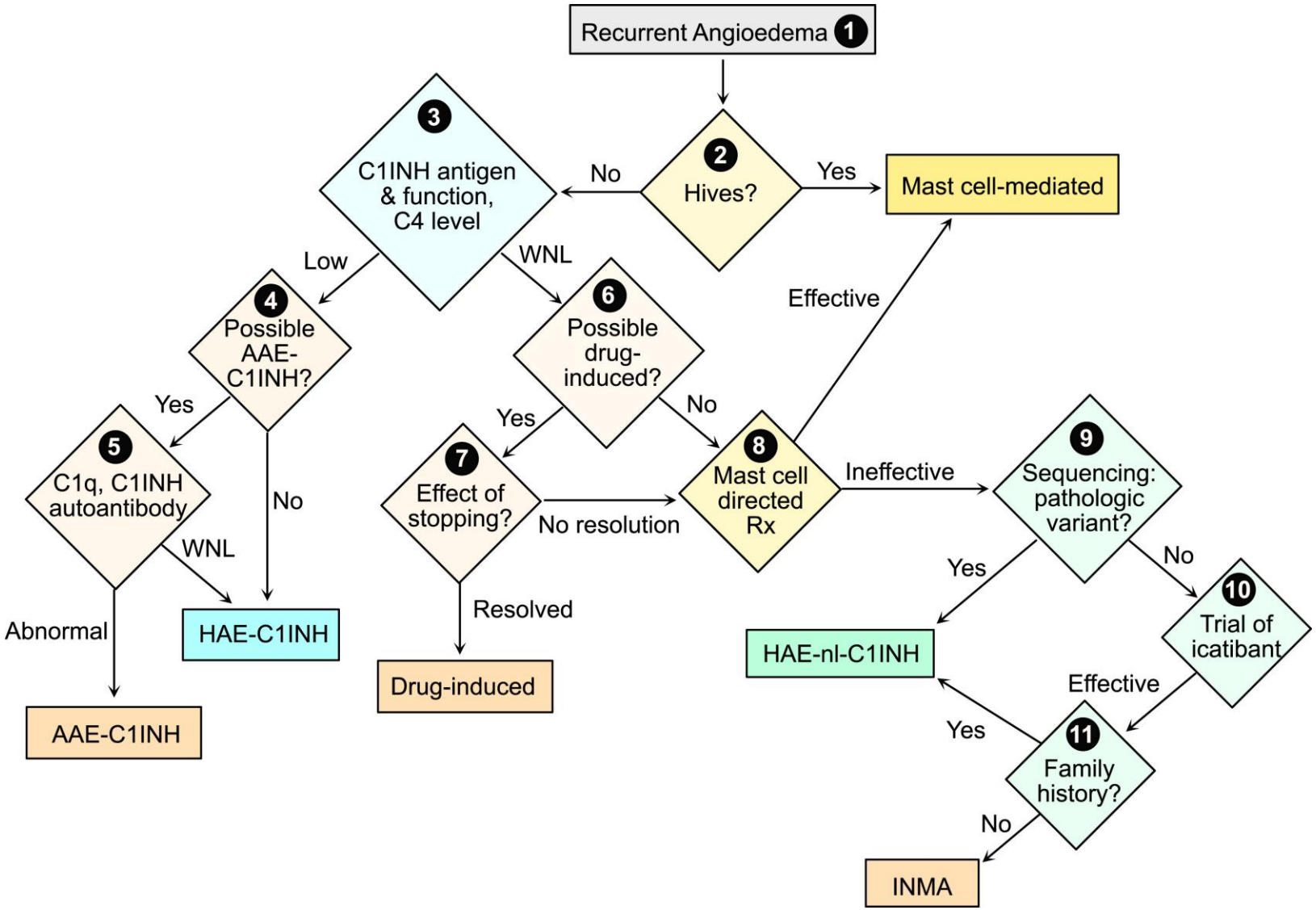
BSACI SpR training day – Cambridge

05.02.2026

Angioedema

- Angioedema is a rapid/slow, often temporary swelling of the deep dermis, subcutaneous, or submucosal tissues
- Dependent oedema / lymphoedema / Eczema
- Typically affecting the face, lips, tongue, throat, eyelids, hands, feet, bowel walls or genitals
- Unlike hives, it involves deeper tissue layers and is caused by fluid leakage from blood vessels

Angioedema

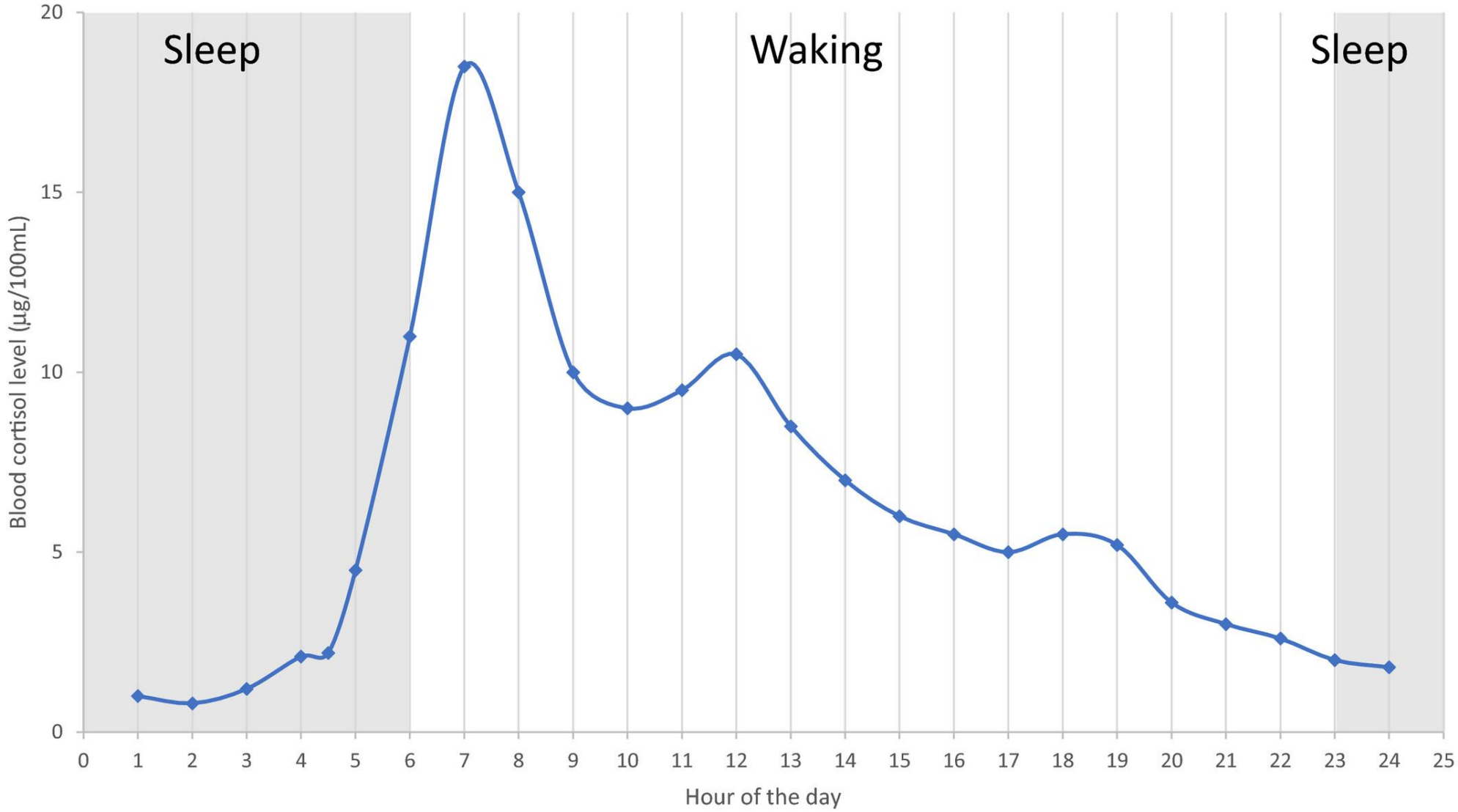


Janina Hahn et al. Bradykinin-Mediated Angioedema Induced by Commonly Used Cardiovascular Drugs*Drugs Drug Candidates* **2023**, *2*(3), 708-727;https://doi.org/10.3390/ddc2030036

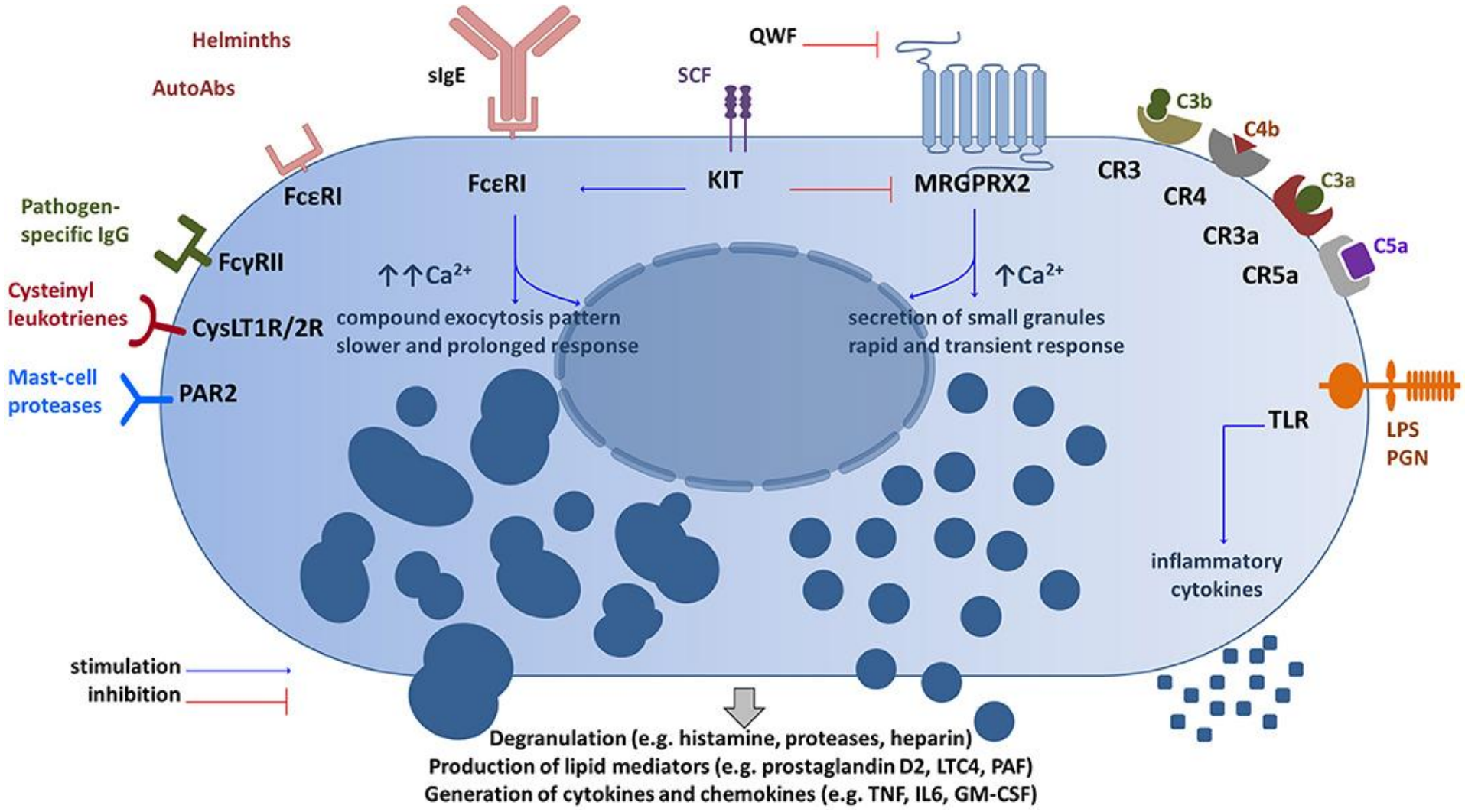
Histamine Vs Bradykinin mediated angioedema - clinical

	Bradykinin mediated	Histamine mediated
Duration	Slow onset and resolution (usually days)	Rapid onset and resolution (usually minutes to hours)
Concomitant hives	No	Often
Gastrointestinal involvement	Yes bowel oedema leading to obstruction	Uncommon
Respiratory involvement	Yes due to laryngeal oedema	Uncommon
Family history	Yes in HAE	No ?yes
Response to adrenalin H1 antihistamines steroids or omalizumab	No	Yes
Response to icatibant or other bradykinin targeted medications	Yes	Yes

Steroid cycle and clinical presentation of angioedema

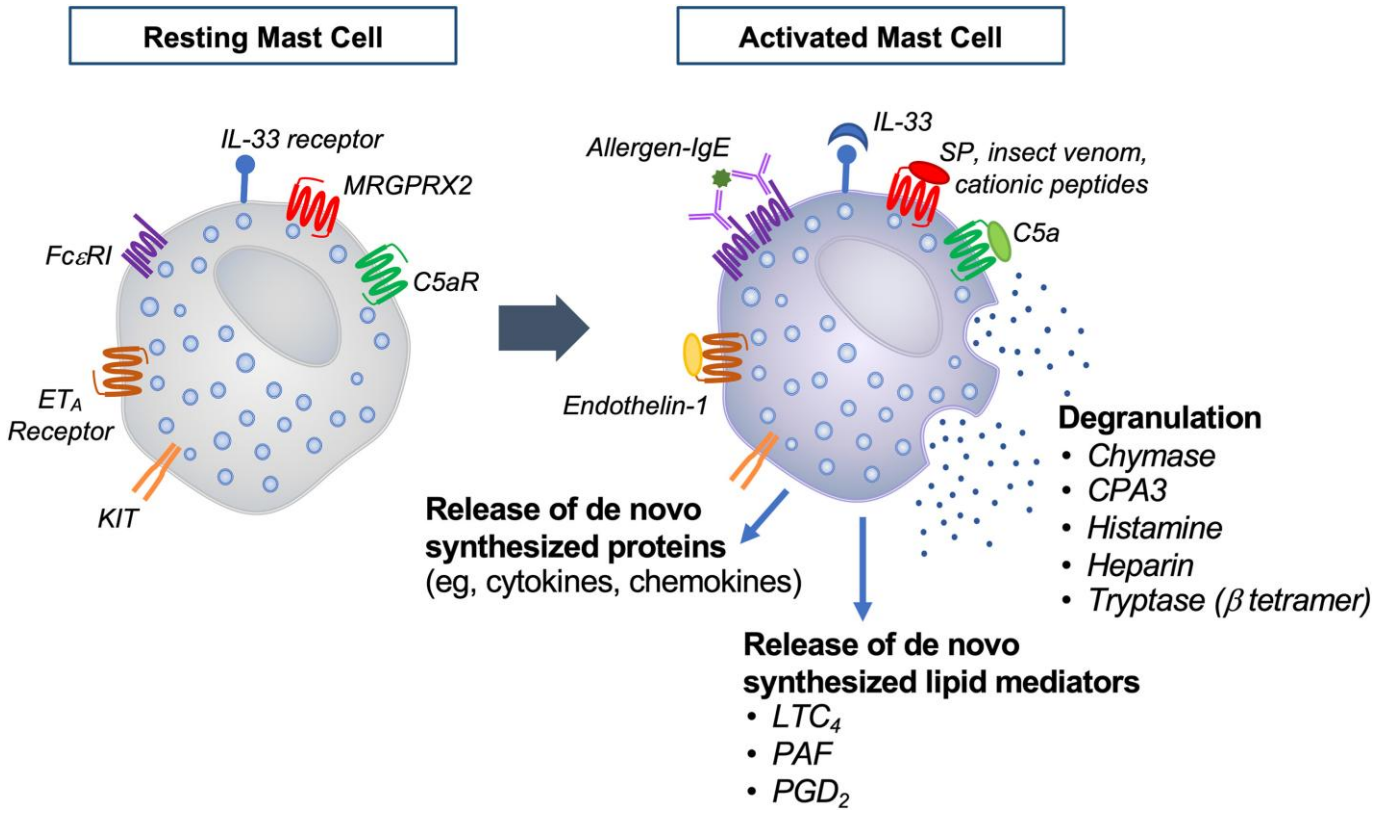


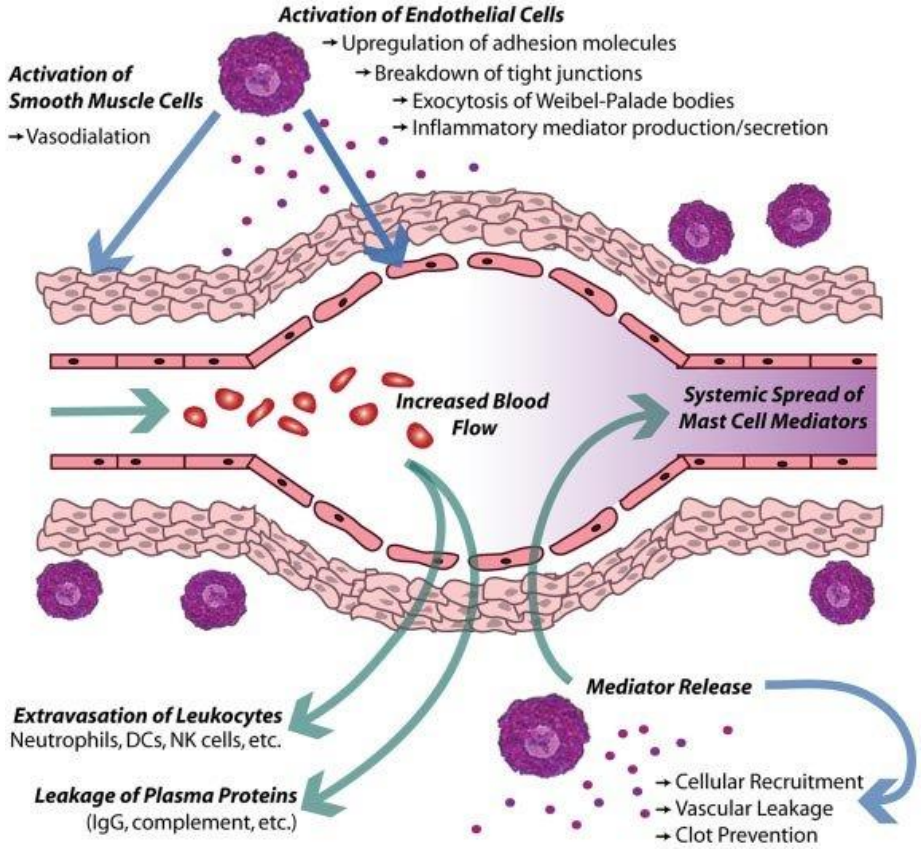
Mast cell mediated angioedema



Grzegorz Porebski[1†]Mas-Related G Protein-Coupled Receptor-X2 (MRGPRX2) in Drug Hypersensitivity ReactionsFront. Immunol., 20 December 2018 Sec. Immunological Tolerance and Regulation Volume 9 - 2018 |

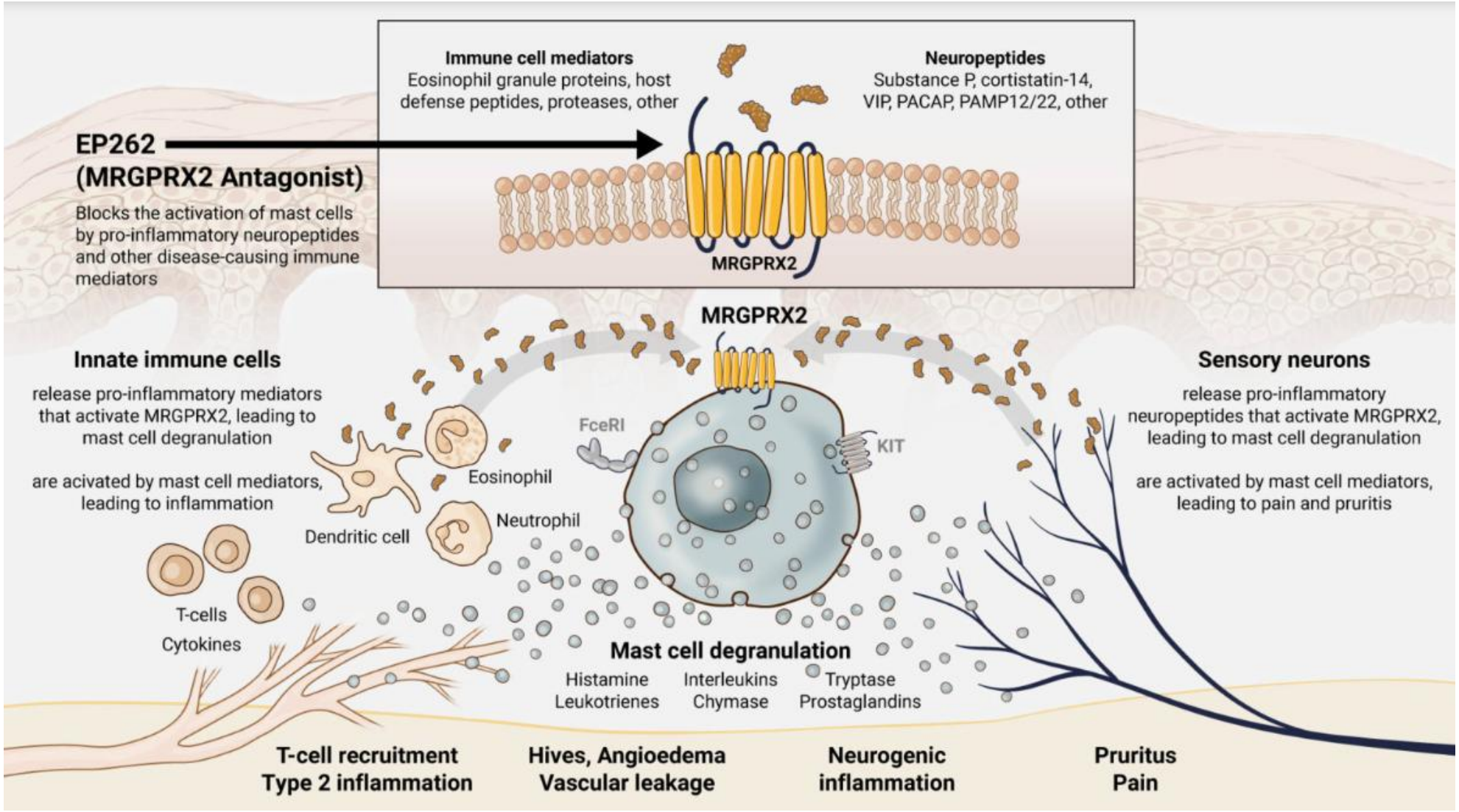
Mast cell mediators and vascular leakage





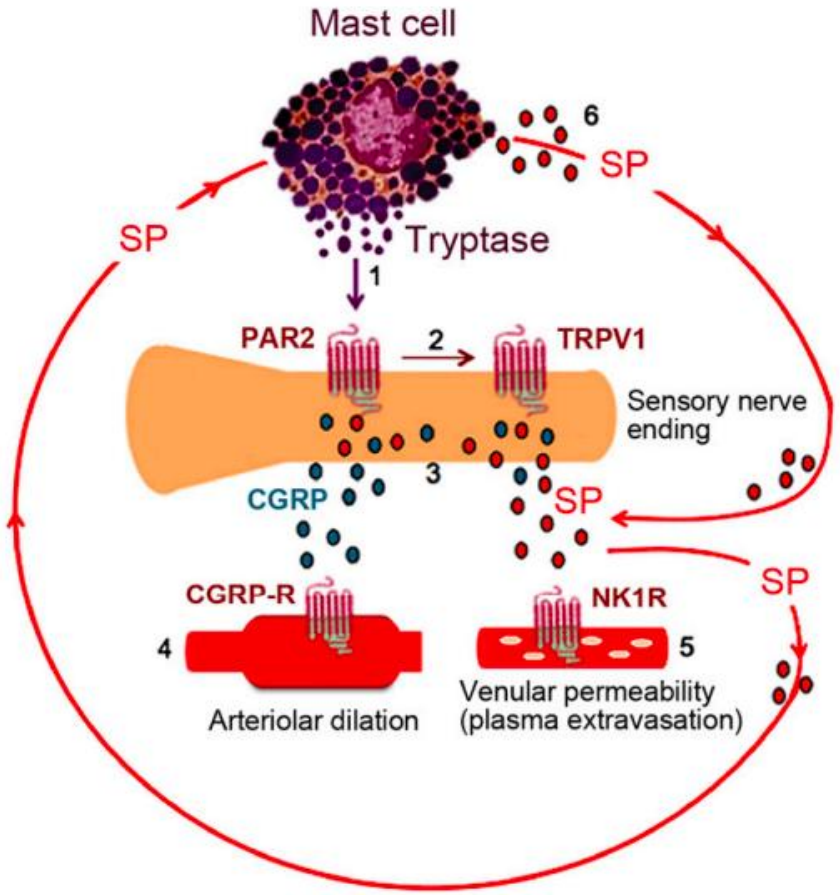
Cem Akin et al. Detecting Changes in Mast Cell Numbers Versus Activation in Human Disease: A Roadblock for Current Biomarkers. The Journal of Allergy and Clinical Immunology: In Practice Volume 12, Issue 7, July 2024, Pages 1727-1737

Mast cell activation by neuronal and immune cells



https://www.escientpharma.com/programs/mrgprx2/

Mast cells sensory nerve positive feedback loop - Angioedema in HAT



1. Activated mast cells contribute to a feed-forward cycle of neuropeptide release
2. Tryptase from mast cells activates PAR2 on the peripheral nerve endings
3. Activation of PAR2 sensitizes transient receptor potential vanilloid 1 (TRPV1)
4. Excited nociceptors stimulate the release of CGRP and SP from the sensory nerve endings
5. CGRP interacts with the type 1 CGRP receptor on arterioles to induce dilatation
6. Substance P activates plasma extravasation via neurokinin 1 (NK1) receptors
7. SP released from nerve endings as well as from mast cells also acts on the mast cells themselves, thus promoting a vicious cycle of mast cell activation.

Lucile Vincent et al. RED CELLS, IRON, AND ERYTHROPOIESIS Mast cell activation contributes to sickle cell pathobiology and pain in mice. Blood 2015; November 5

Hereditary alpha tryptasaemia (HAT)

1. There is a significant upregulation of the Mas-related G protein-coupled receptor-X2 (MRGPRX2) on mast cells, particularly within the gastrointestinal (GI) tract.
2. This increase in MRGPRX2 expression is associated with elevated mast cell (MC) density and heightened mast cell-mediated symptoms in HAT patients, such as chronic diarrhea, abdominal pain, and increased susceptibility to anaphylaxis.
3. In our cohort of 34 patients – higher the copy number higher the incidence of angioedema

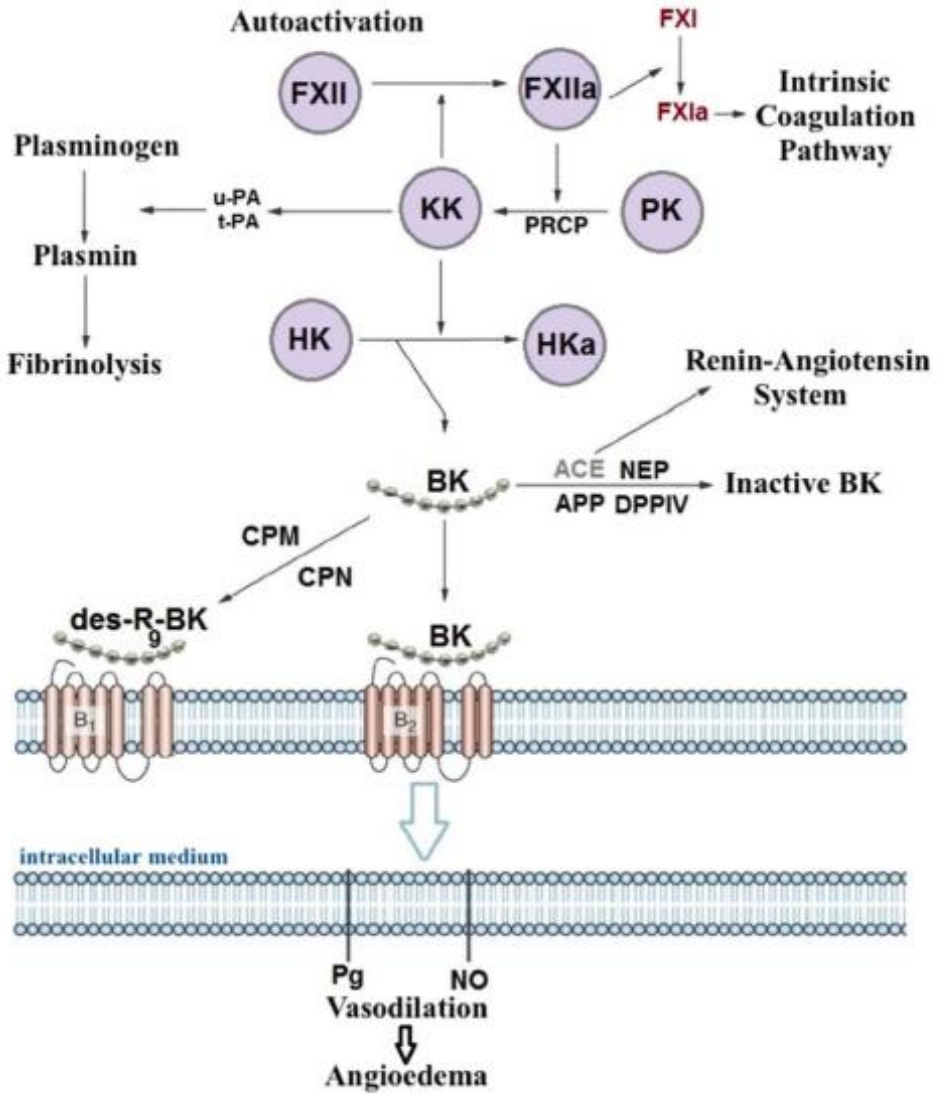
https://www.escientpharma.com/programs/mrgprx2/

Angioedema

TABLE III. Differences in presentation between bradykinin-mediated and mast cell–mediated angioedema

Parameter	Bradykinin-mediated angioedema	Mast cell–mediated angioedema
Severity of swelling	Often severe and disfiguring; may be incapacitating	Mild to moderate swelling in most cases
Frequency of swelling (untreated)	Variable, averaging 2/mo	Variable but may occur daily
Duration of untreated swelling	Typically, 3-5 d	Typically, 1-2 d
Location of swelling	Extremities = abdominal > face > genital	Face > extremities >> abdominal
Frequency of abdominal attacks	High, typically 50% of attacks	Rare
Risk of asphyxiation from laryngeal attack	High	Low (unless anaphylaxis)
Response to antihistamines, corticosteroids, or epinephrine	Poor	Good

Bradykinin production



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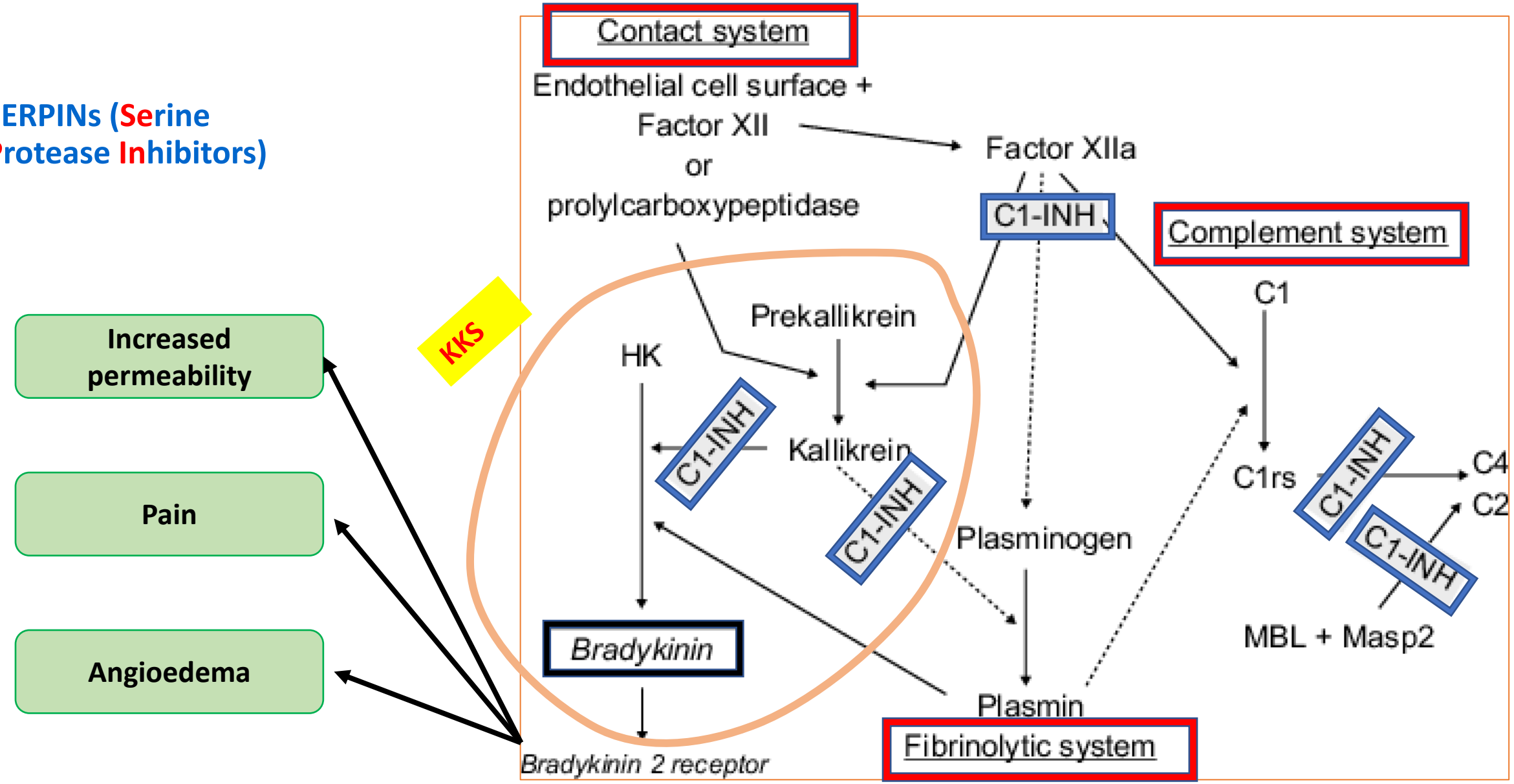
Pathophysiology of angioedema in HAE

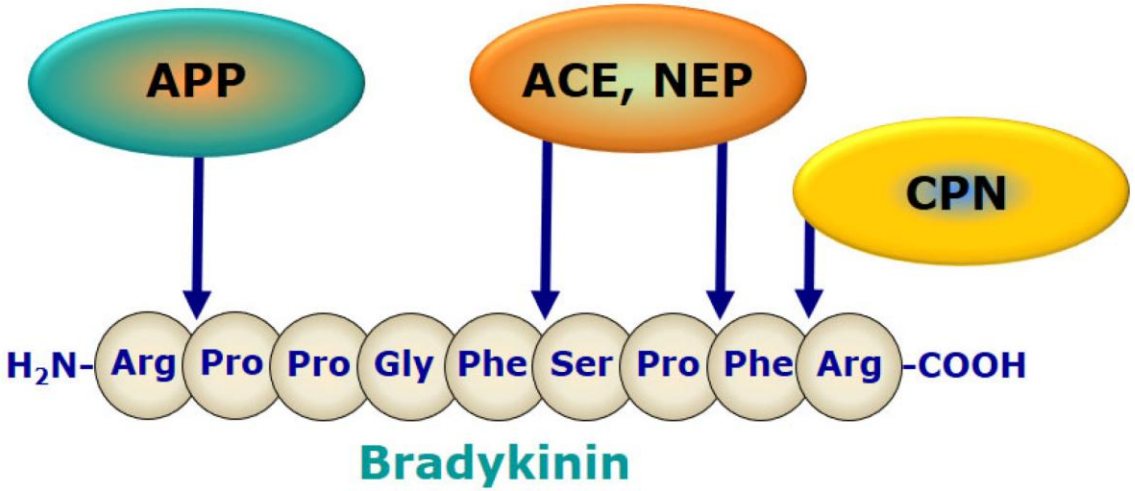
SERPINs (Serine Protease Inhibitors)

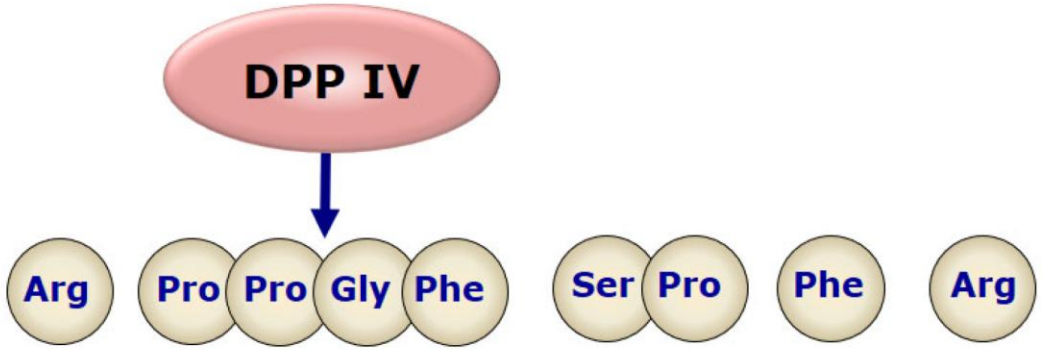


Benjamin Davis et al. Therapeutics and Clinical Risk Management, 2011

Bradykinin metabolism

- Aminopeptidase P (APP)
- Angiotensin-Converting Enzyme (ACE)
- Neutral Endopeptidase (NEP)
- Nephrilysin
- Carboxypeptidase N convert bradykinin to des-Arg9 bradykinin
- Carboxypeptidase M convert bradykinin to des-Arg9 bradykinin





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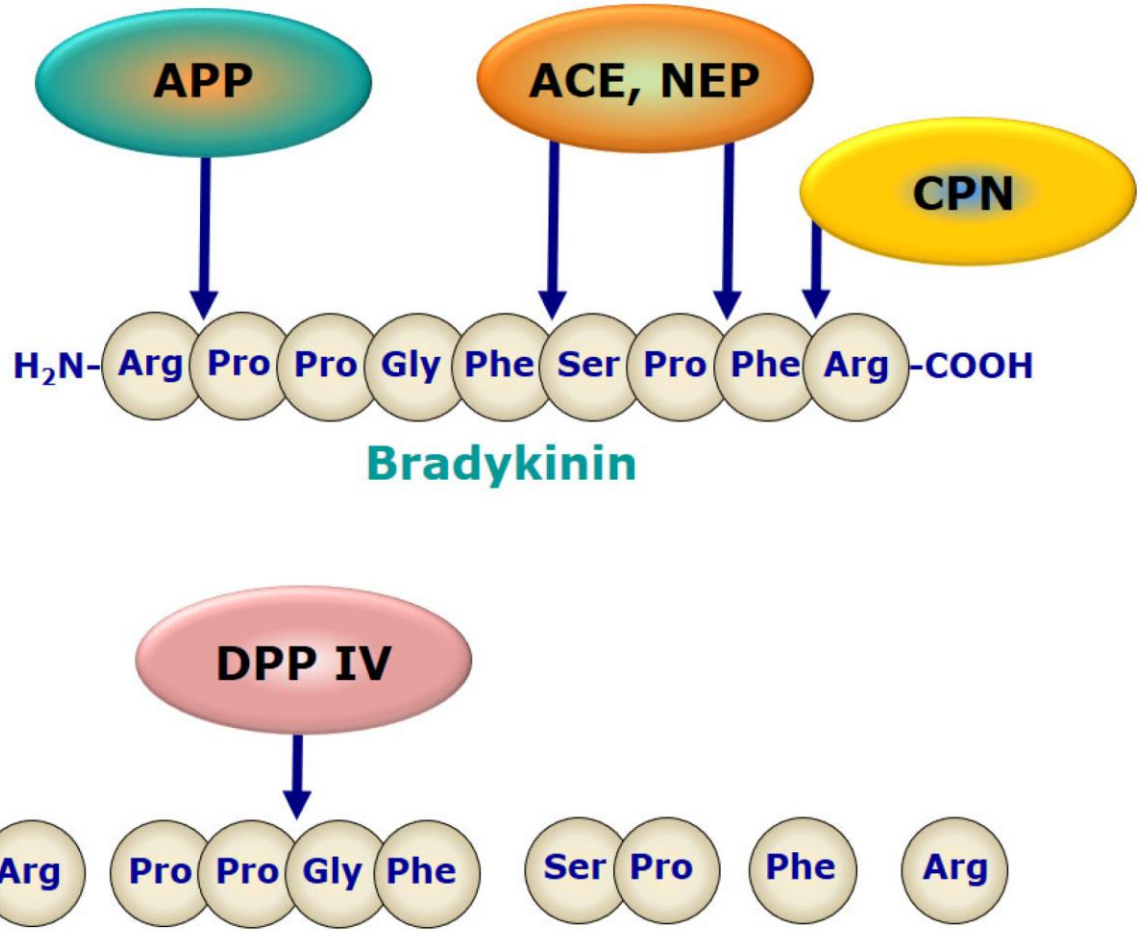
Bradykinin metabolism

1. Dipeptidyl peptidase IV (DPP IV) cannot hydrolyze bradykinin directly because of its binding properties to the substrate amino acids

2. Binds to inactive residual peptide bradykinin$_{2–9}$ after cleavage of the N-terminal Arg



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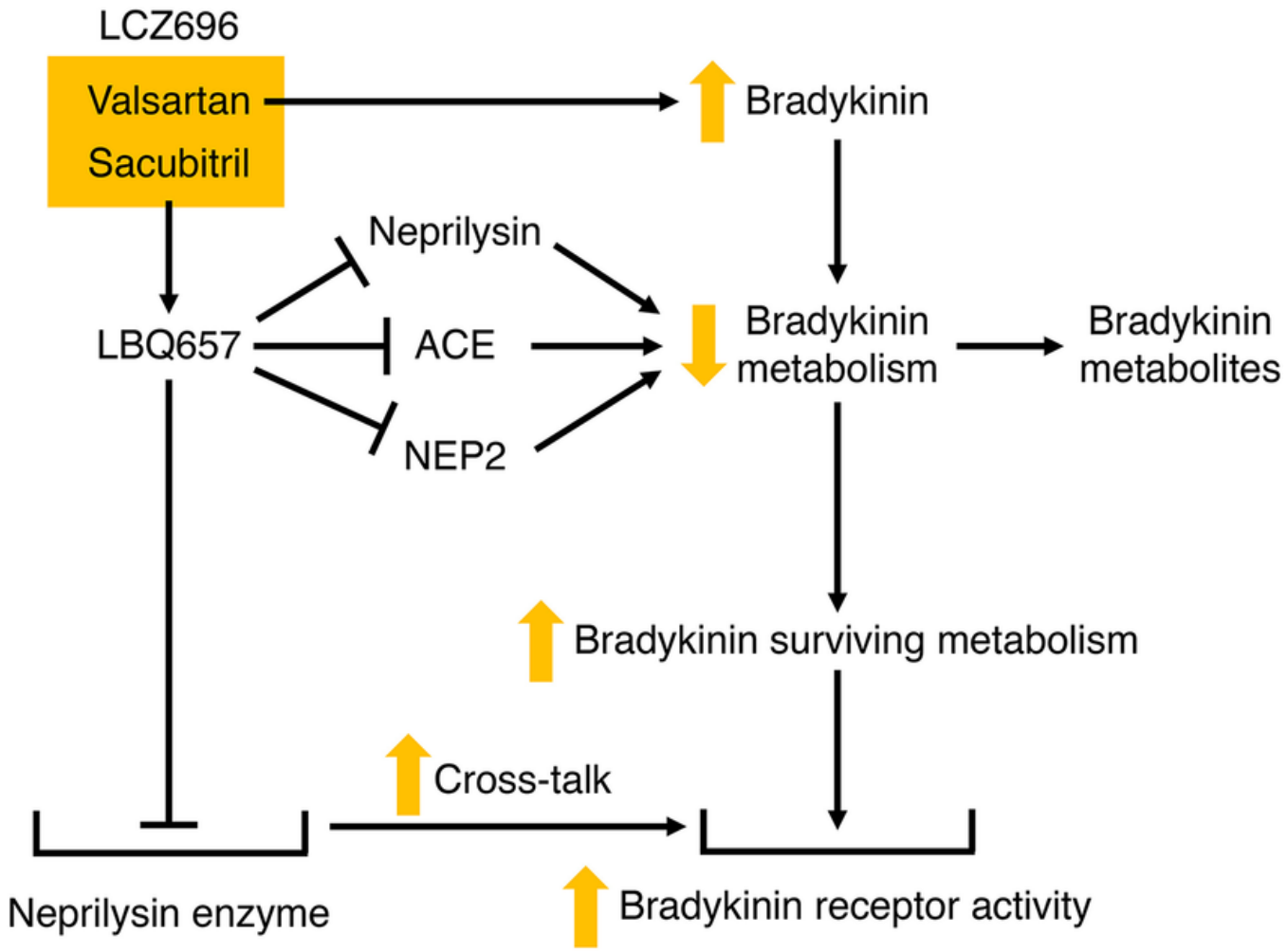
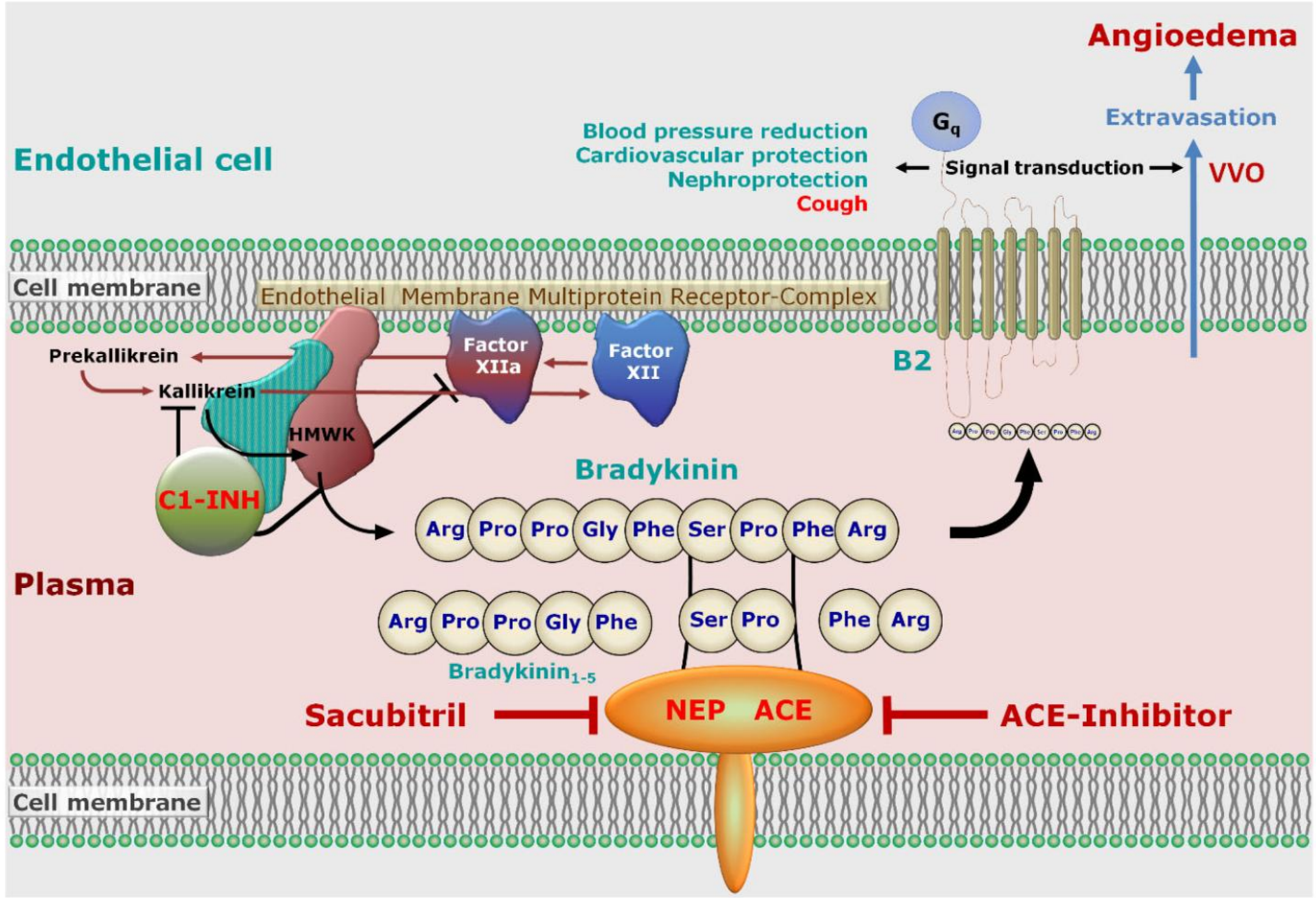
Drug induced angioedema

- NSAIDs/Opioids
- ACEI
- GLP-1 inhibitors
- Neprilysin inhibitors (Sacubitril)



Duncan J Campbell Neprilysin Inhibitors and Bradykinin. Front Med (Lausanne) 2018 Sep 19:5:257.

Bradykinin on endothelium

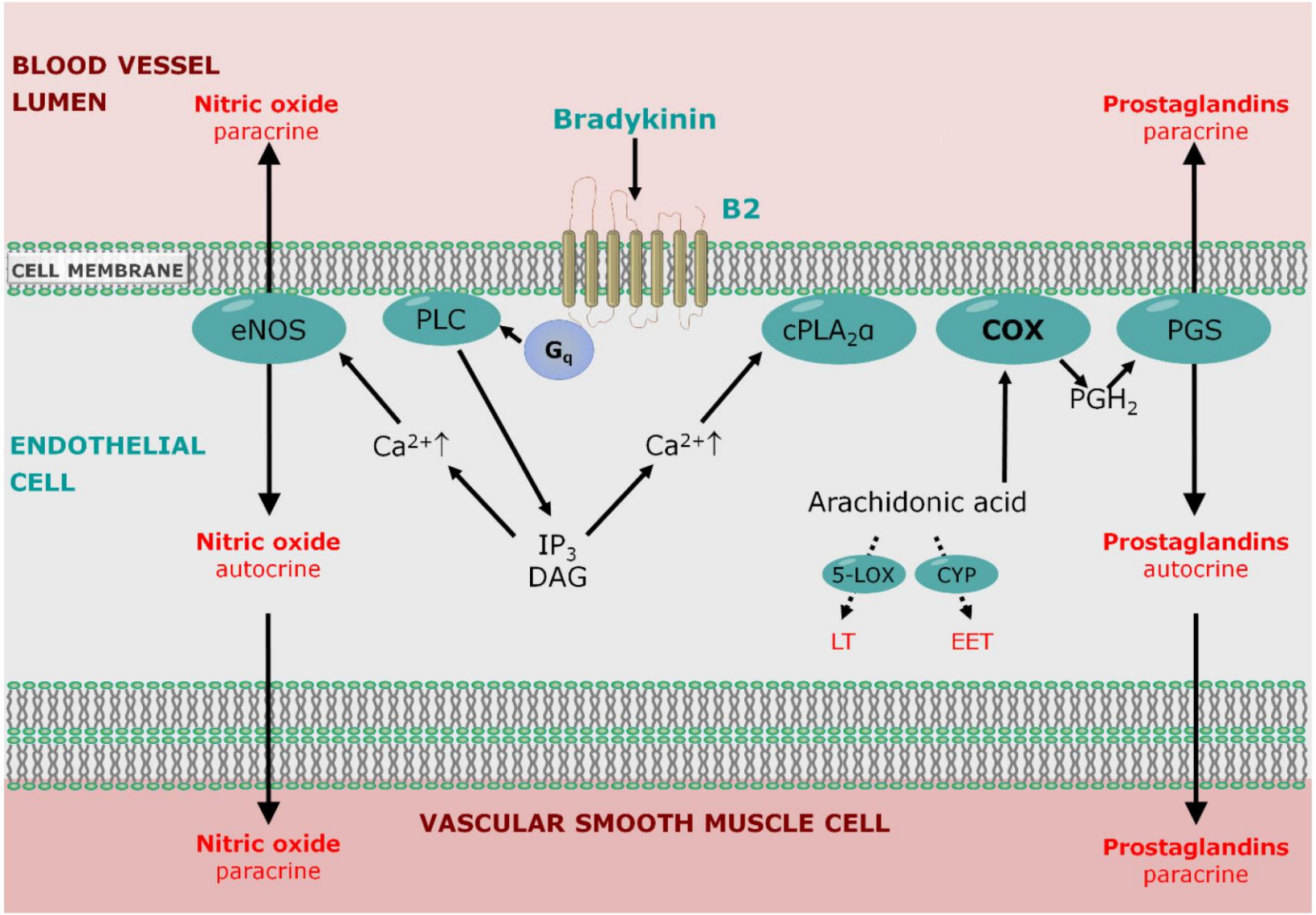


1. Once synthesized, bradykinin activates the constitutively expressed G-protein coupled (Gq) bradykinin receptor type 2 (B2)

2. Many effects of bradykinin are mediated mainly by B2 activation on endothelial cells, resulting in the release of NO, prostacyclin (PGI_2), and endothelial hyperpolarization factor (EDHF)

Janina Hahn et al. Bradykinin-Mediated Angioedema Induced by Commonly Used Cardiovascular Drugs*Drugs Drug Candidates* **2023**, *2*(3), 708-727;https://doi.org/10.3390/ddc2030036

B2 receptor mediated NO and prostaglandin release



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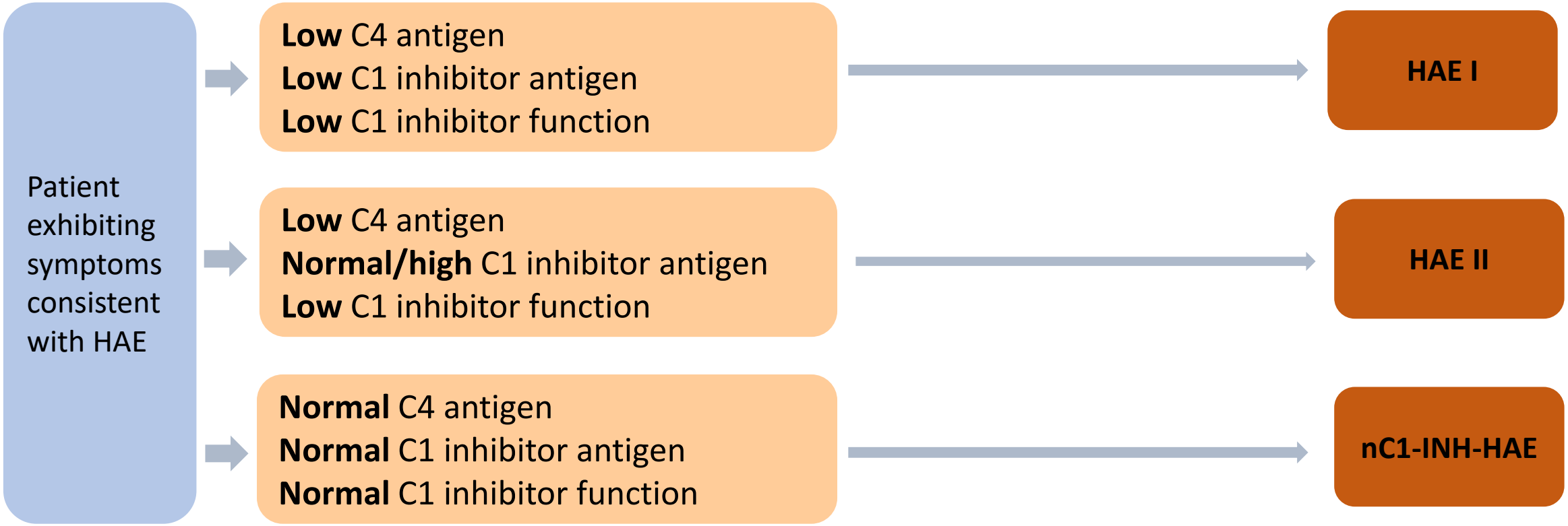
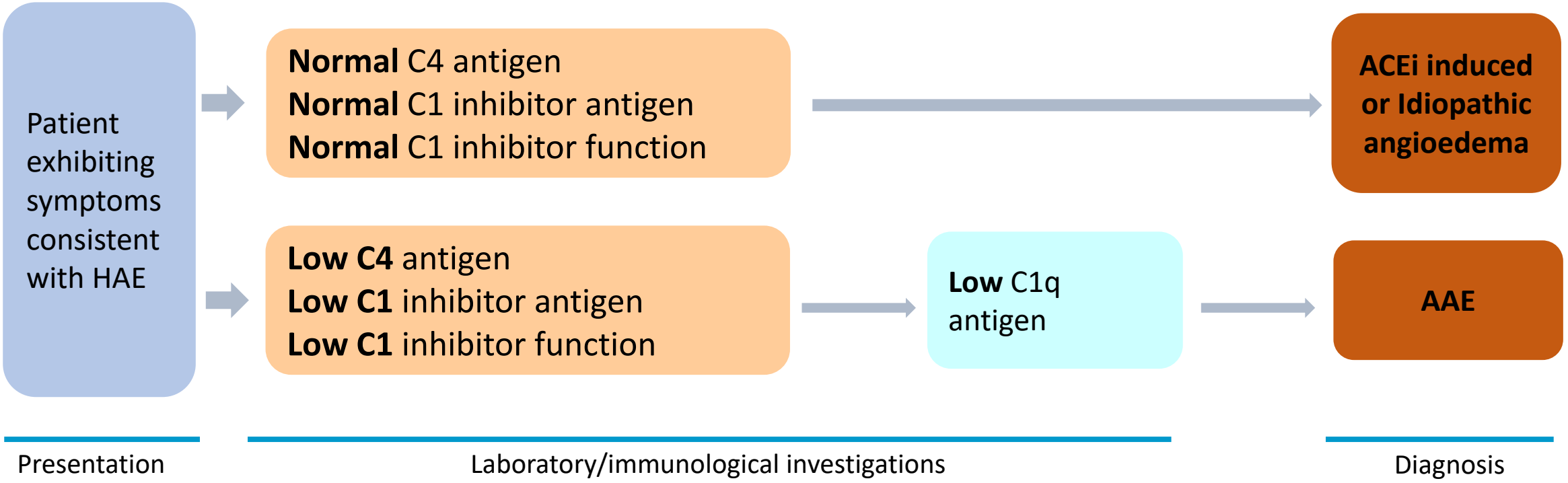
Classification of Hereditary angioedema



Other bradykinin mediated angioedema



Acquired angioedema in LPD/MGUS and autoimmune diseases/SLE

- LPD/MGUS produce monoclonal immunoglobulins directly trigger activation of classical pathway complement system – over consumption of C1-INH
- Monoclonal also forms immune complexes that activates classical pathway complement system – over consumption of C1-INH
- LPD/MGUS produce C1 INH auto antibodies - approximately 50% of patients
- These autoantibodies target the functional sites of C1-INH, leading to its inactivation/neutralization and rapid consumption
- SLE – auto antibodies - neutralization and destruction, immune complex formation and constant classical pathway activation leads to consumptive deficiency of C1INH

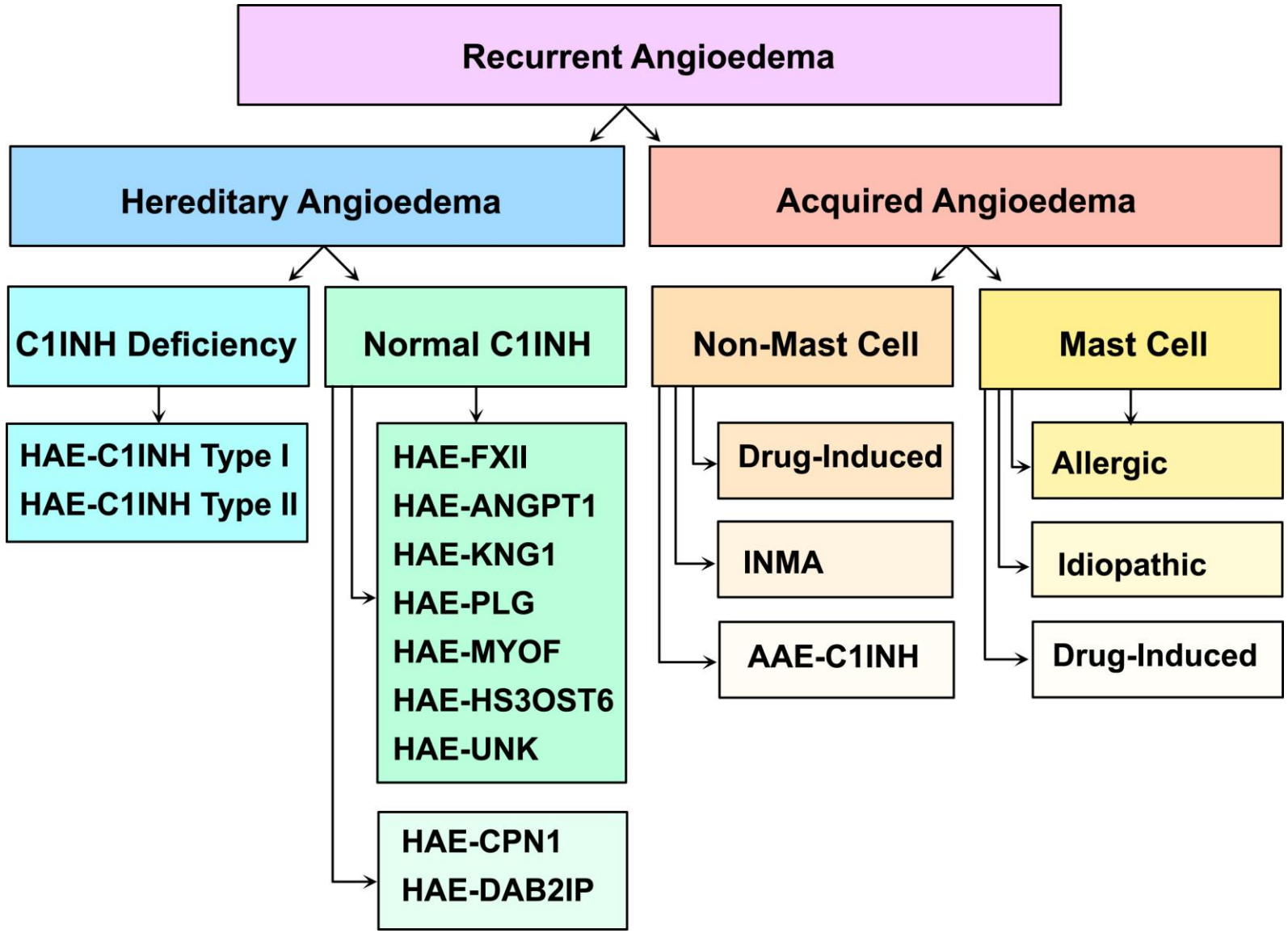
Classification of hereditary angioedema

TABLE I. Genes with pathogenic variants linked to HAE-C1INH, HAE-nl-C1INH, and FACAS

Disorder	Gene	OMIM No.	Protein	Complementary DNA	Protein	Reference
HAE-C1INH	*SerpinG1*	106100	C1INH	many	many	8
HAE-FXII	*F12*	610618	Coagulation FXII	c.983C>A	p.Thr328Lys	14
HAE-FXII	*F12*	610618	Coagulation FXII	c.983C>G	p.Thr328Arg	14
HAE-FXII	*F12*	610618	Coagulation FXII	c.971_1018+24 del72	del	15
HAE-FXII	*F12*	610618	Coagulation FXII	c.892_909dup	p.Pro298_Pro303dup	16
HAE-PLG	*PLG*	619360	Plasminogen	c.988A>G	p.Lys330Glu	17
HAE-KNG1	*KNG1*	619363	Kininogen	c.1136T>2	p.Met379Lys	18
HAE-ANGPT1	*ANGPT1*	619361	Angiopoietin 1	c.807G>T	p.Ala119Ser	19
HAE-MYOF	*MYOF*	619366	Myoferlin	c.651G>T	p.Arg217Ser	20
HAE-HS3OST6	*HS3OST6*	619367	3-OST-6	c.430A>T	p.Thr144Ser	21
HAE-CPN1	*CPN1*	Not available	Carboxypeptidase N	c.533G>A	p.Gly178Asp	22
HAE-CPN1	*CPN1*	Not available	Carboxypeptidase N	c.582A>G	p.Glu194= (splice)	22
HAE-CPN1	*CPN1*	Not available	Carboxypeptidase N	c.734C>T	p.Thr245Met	22
HAE-DAB2IP	*DAB2IP*	Not available	Disabled homology 2 interacting protein	c.715G>A	p.Asp239Asn	23
FACAS	*F12*	Not available	Coagulation FXII	c.859T>A	p.Trp268Arg	24

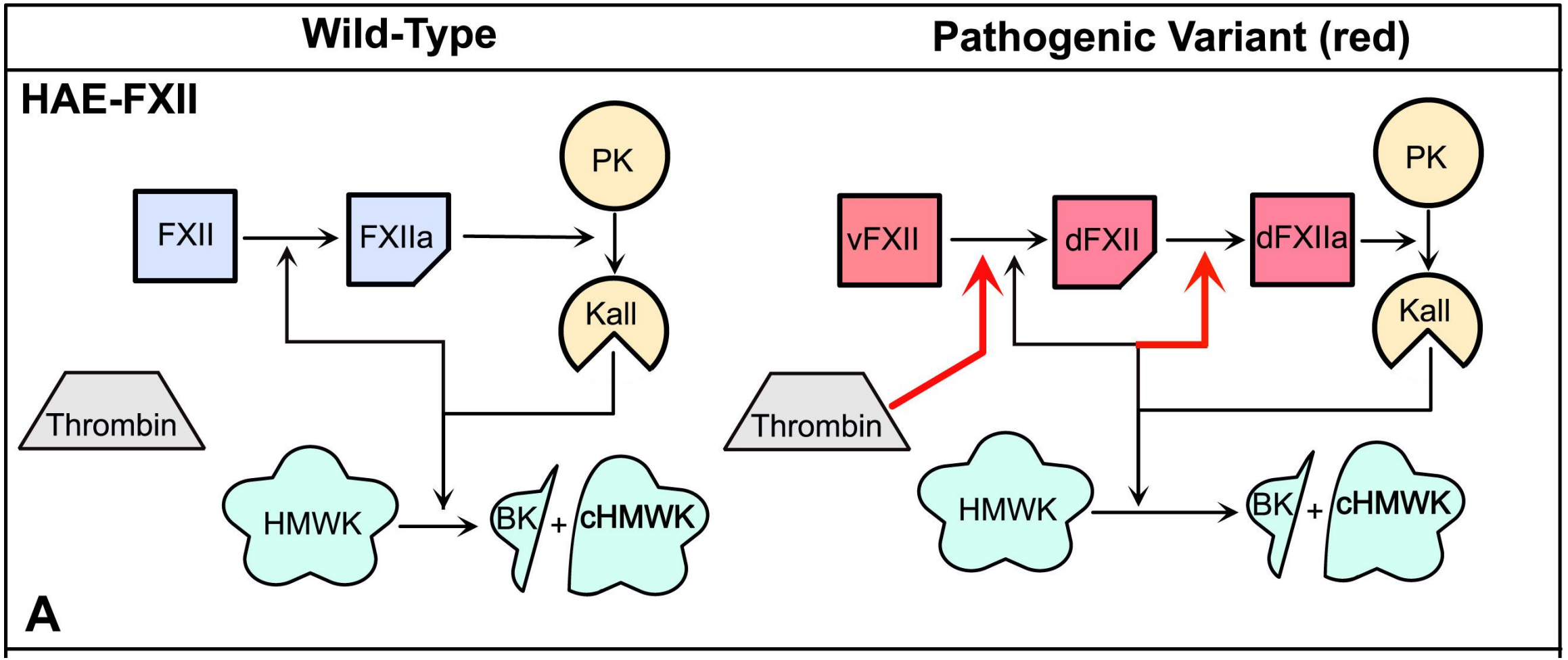
C1INH, C1 inhibitor; *HAE*, hereditary angioedema; *HAE-ANGPT1*, HAE due to a variant in the *ANGPT1* gene; *HAE-C1INH*, HAE due to C1INH deficiency; *HAE-CPN1*, HAE due to a variant in the *CPN1* gene; *HAE-DAB2IP*, HAE due to a variant in the *DAB2IP* gene; *HAE-FXII*, HAE due to a variant in the *F12* gene; *HAE-HS3OST6*, HAE due to a variant in the *HS3OST6* gene; *HAE-KNG1*, HAE due to a variant in the *KNG1* gene; *HAE-MYOF*, HAE due to a variant in the *MYOF* gene; *HAE-PLG*, HAE due to a variant in the *PLG* gene; *FACAS*, coagulation factor XII–associated cold autoinflammatory syndrome.

Angioedema



Sandra C. Christiansenet al. Hereditary Angioedema With Normal C1 Inhibitor: A Quarter Century of Forward Progress and Persisting ObstaclesJ ALLERGY CLIN IMMUNOL PRACT VOLUME 13, NUMBER 6: 1300-1309

Factor XII GOF



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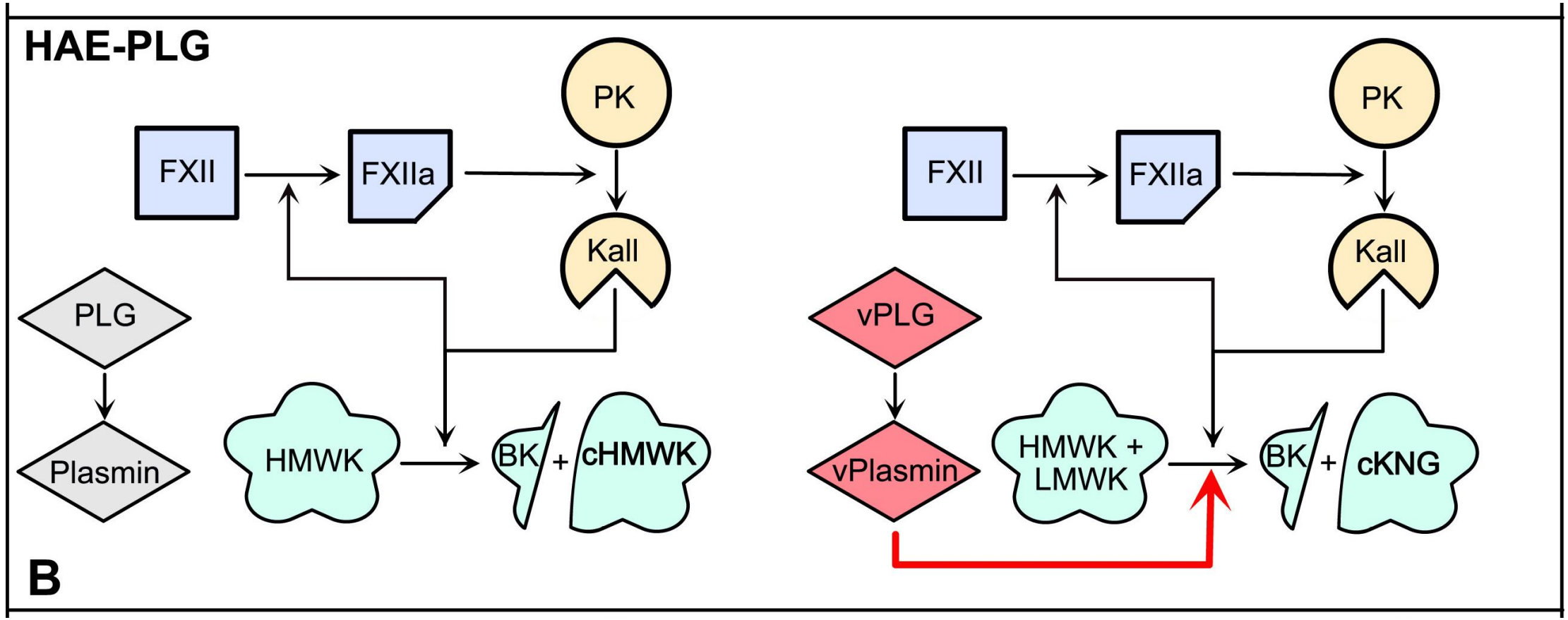
Plasminogen GOF



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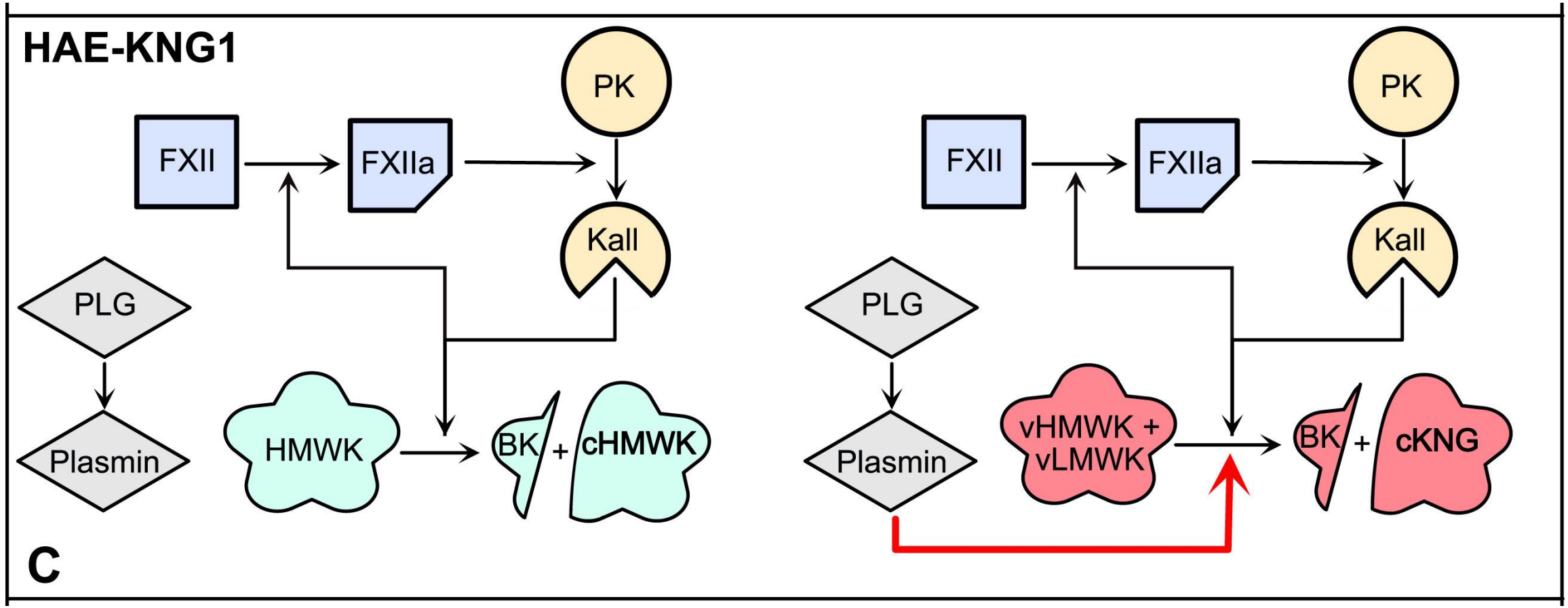
KNG1 – GOF



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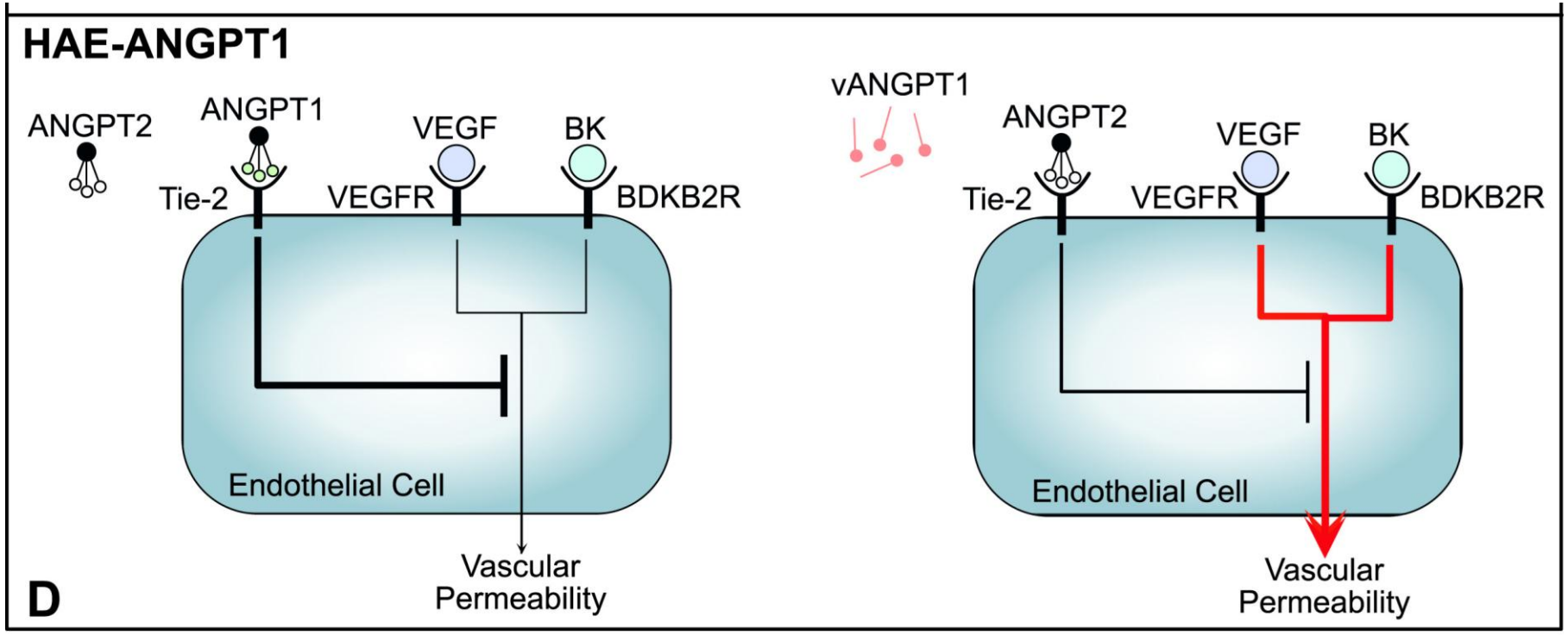
ANGPT1



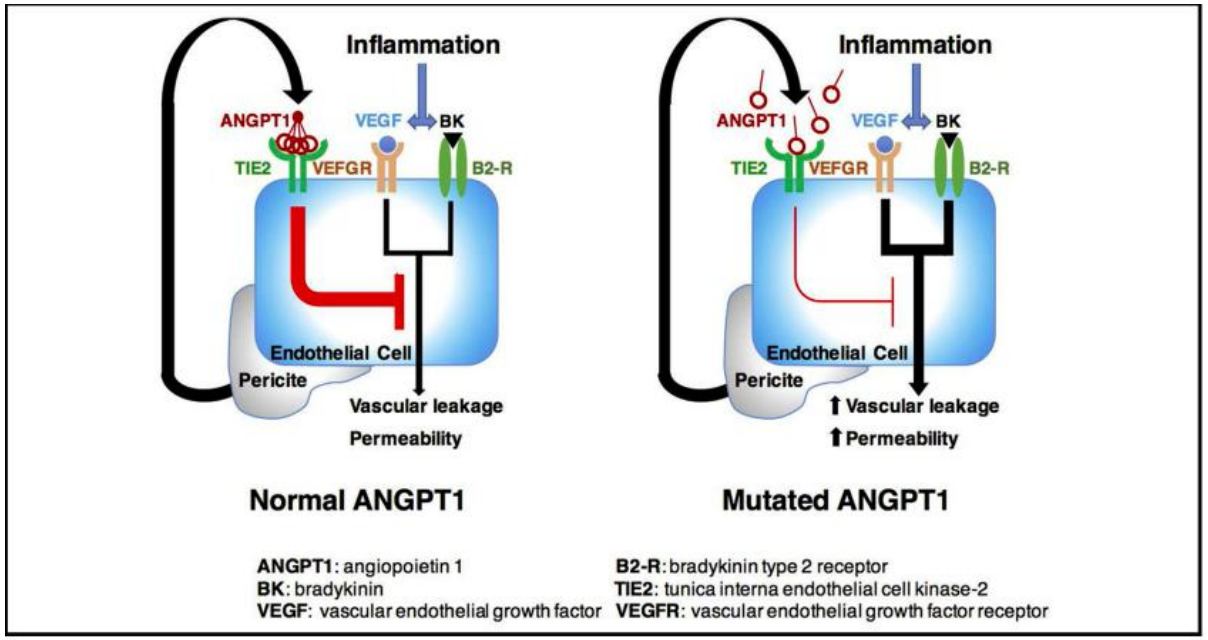
- ANGPT1 activates TIE2 for stability; ANGPT2 usually inhibits TIE2, inducing vessel plasticity.

- An increased ANGPT2/ANGPT1 ratio is a marker of vascular instability, driving angiogenesis or pathological leakage.

nC1-INH-HAE with *ANGPT1*

Mutation of the angiopoietin-1 gene *(ANGPT1)* associates with a new type of hereditary angioedema

Valeria Bafunno, MSc, PhD,[a*] Davide Firinu, MD,[b*] Maria D'Apolito, MSc, PhD,[a] Giorgia Cordisco, BSc,[a] Stefania Loffredo, MD,[c] Angelica Leccese, BSc,[a] Maria Bova, MD,[c] Maria Pina Barca, MD,[b] Rosa Santacroce, MSc, PhD,[a] Marco Cicardi, MD,[d] Stefano Del Giacco, MD,[b‡] and Maurizio Margaglione, MD[a‡] *Foggia, Cagliari, Naples, and Milan, Italy*



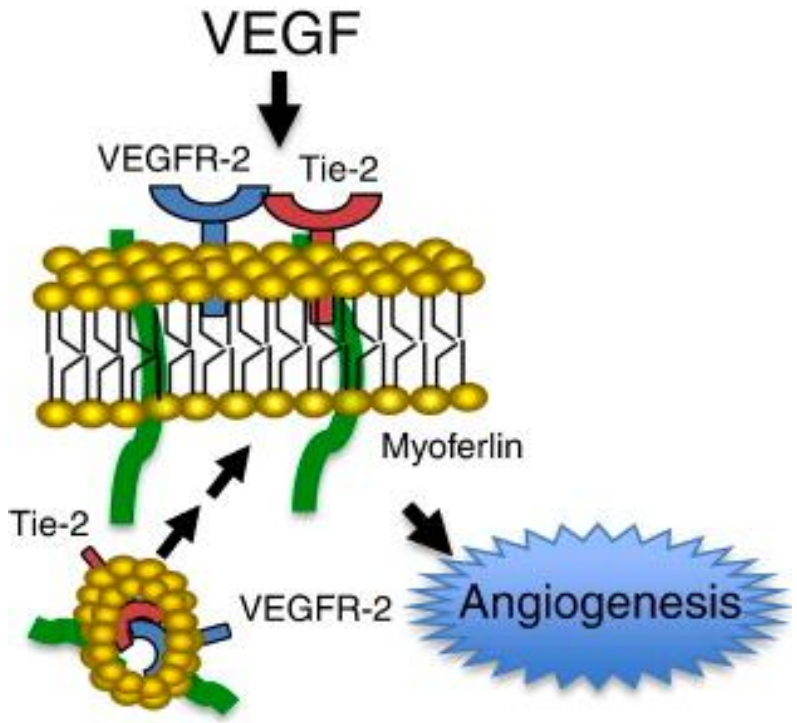
- *ANGPT1* mutations leads to reduced binding of the ANGPT1 protein to its receptor, TIE2, and a reduction in the multimeric forms
- of the protein that disrupt vascular endothelial cell stability and leads to increased vascular permeability
- ANGPT2 antagonizes ANGPT1 leading to enhanced vascular permeability
- ANGPT1/ ANGPT2 was found to be low in p.Ala119Ser mutation

nC1-INH-HAE with *Myoferlin mutations*

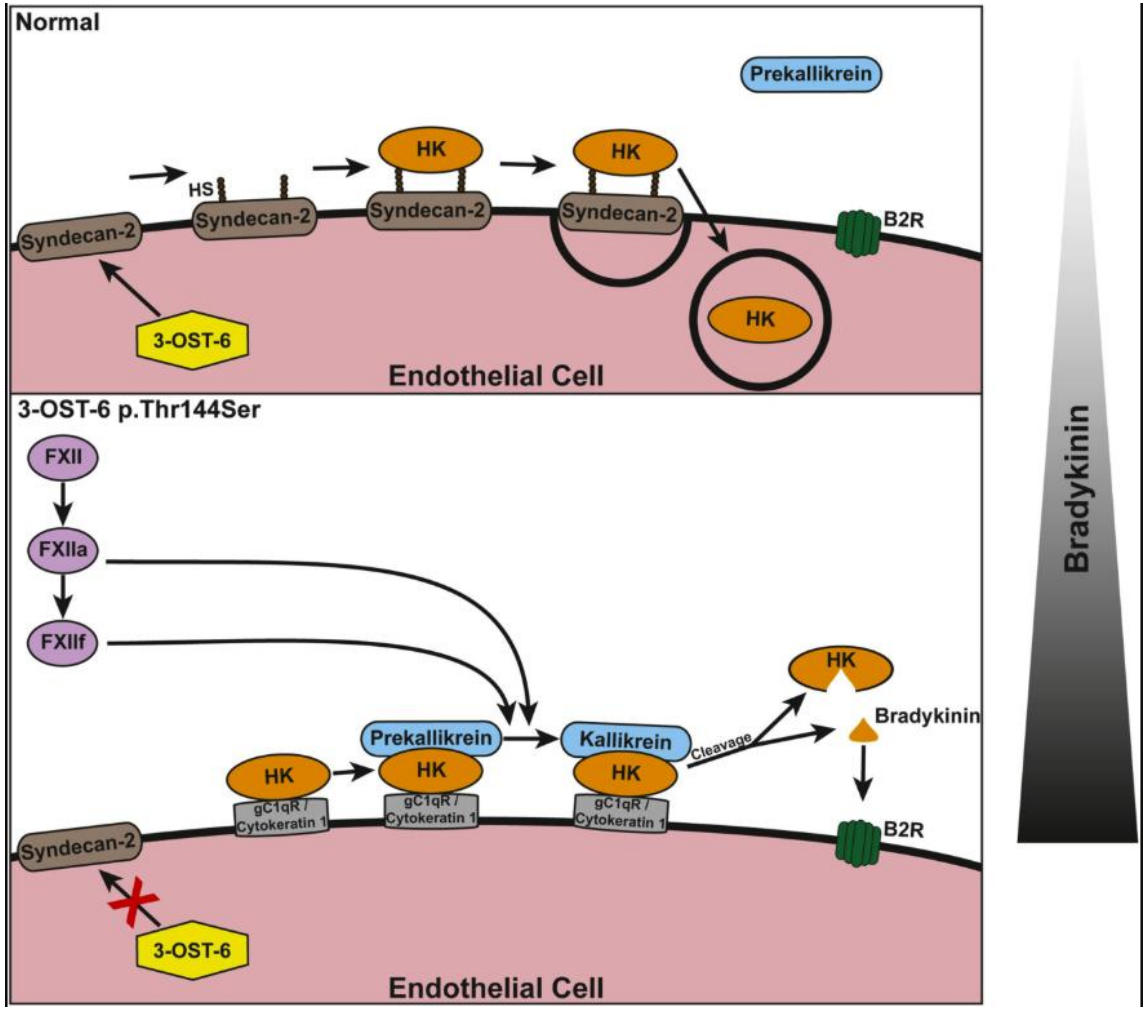
Vascular Pharmacology
Volume 55, Issues 1–3, July–September 2011, Pages 26-33

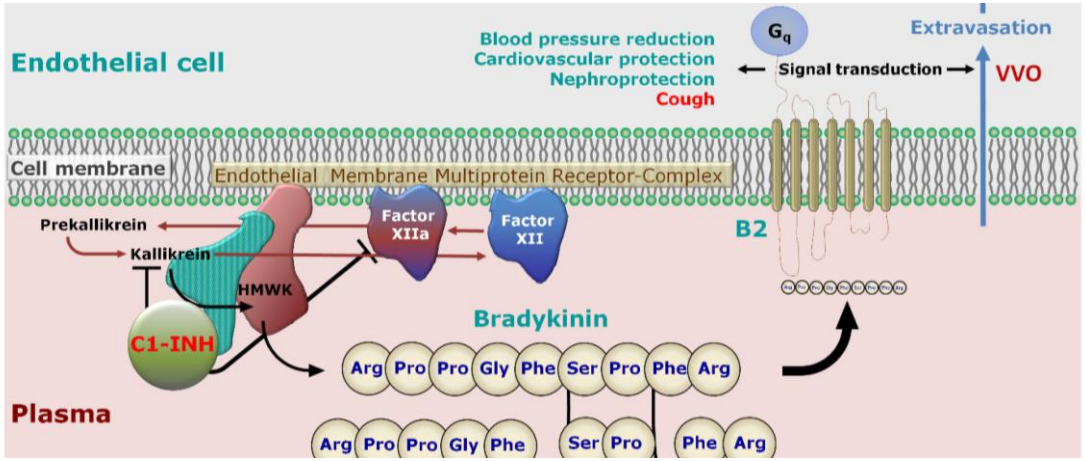
Myoferlin gene silencing decreases Tie-2 expression in vitro and angiogenesis in vivo

Carol Yu, Arpeeta Sharma, Andy Trane, Soraya Utokaparch, Cleo Leung, Pascal Bernatchez



HSST mutation and angioedema

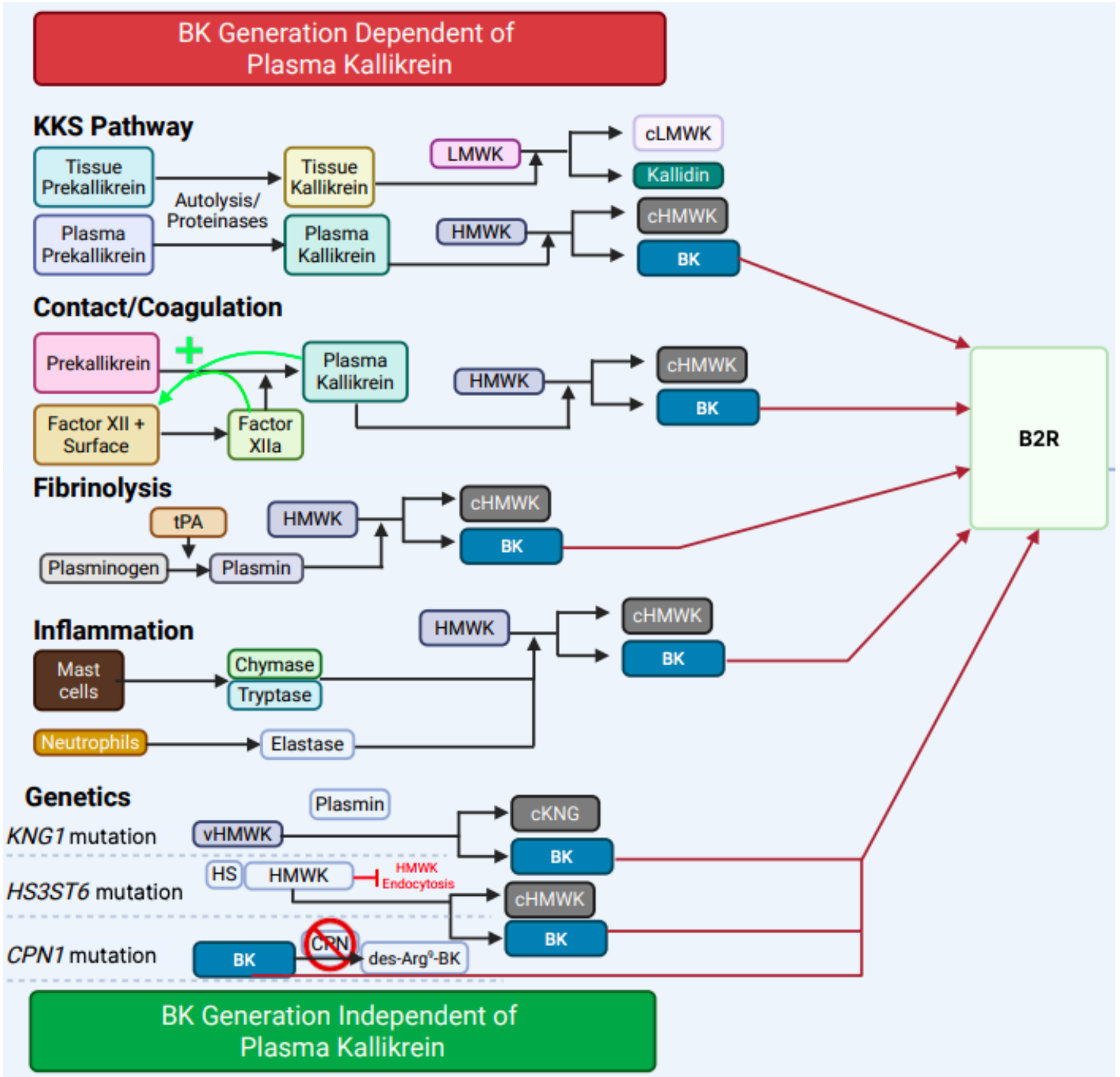




In normal endothelial cells, HS acts on syndecan-2 results in specific interaction of HK on the cellular surface by direct interaction followed by endocytosis and prevents HK cleavage by kallikrein

The mutated HS-glucosamine 3-OST-6 cannot perform the last step of syndecan-2 O-sulfationthe cellular surface or its intern, which in turn affects either the binding of HK on alization via endocytosis

Konrad Bork, et al. Novel hereditary angioedema linked with a heparan sulfate 3-O-sulfotransferase 6 gene mutation. ALLERGY CLIN IMMUNOL 2021



https://www.emjreviews.com/wp-content/uploads/2023/09/Bradykinin-Mediated-Angioedema-Pathways-Physiology-and-Disease-Mechanism.pdf

nC1-INH-HAE with *FXII mutations*

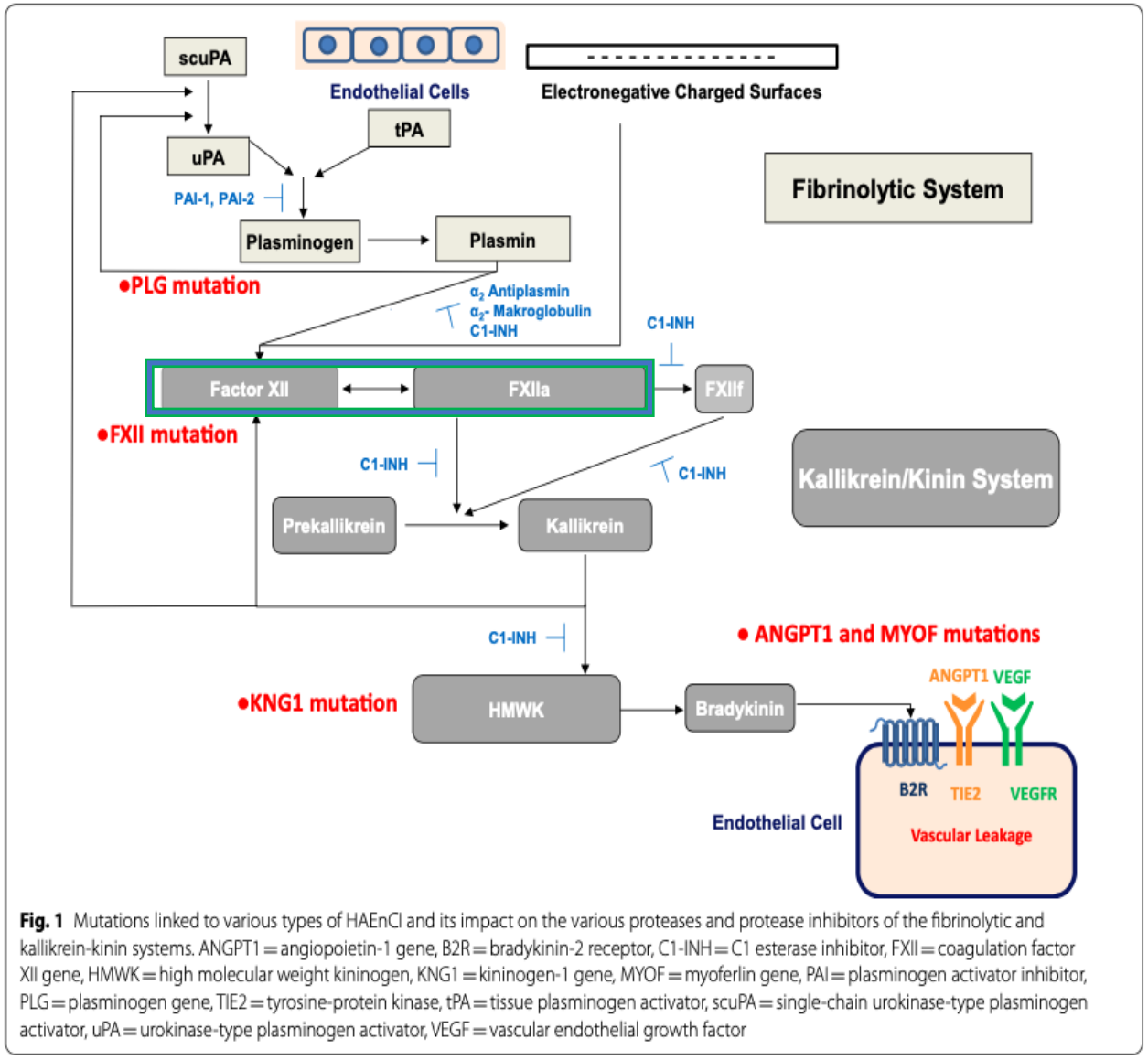


Fig. 1 Mutations linked to various types of HAEnCI and its impact on the various proteases and protease inhibitors of the fibrinolytic and kallikrein-kinin systems. ANGPT1 = angiopoietin-1 gene, B2R = bradykinin-2 receptor, C1-INH = C1 esterase inhibitor, FXII = coagulation factor XII gene, HMWK = high molecular weight kininogen, KNG1 = kininogen-1 gene, MYOF = myoferlin gene, PAI = plasminogen activator inhibitor, PLG = plasminogen gene, TIE2 = tyrosine-protein kinase, tPA = tissue plasminogen activator, scuPA = single-chain urokinase-type plasminogen activator, uPA = urokinase-type plasminogen activator, VEGF = vascular endothelial growth factor

- AD GOF
- Over 400 patients to date
- Acts via kallikrein and plasmin
- Effect of anti-fibrinolytic medications in this type of HAE – tranexamic acid
- The promoters of *FXII* and oestrogen responsive element (*ERE*) genes are similar but not identical
- Oestrogen precipitates attacks by enhancing FXII in plasma
- Female predominance, aggravation in pregnancy and oestrogen dependency

Bork *et al. Orphanet J Rare Dis (2020) 15:289* :11 of 14

nC1-INH-HAE with *PLG mutations*

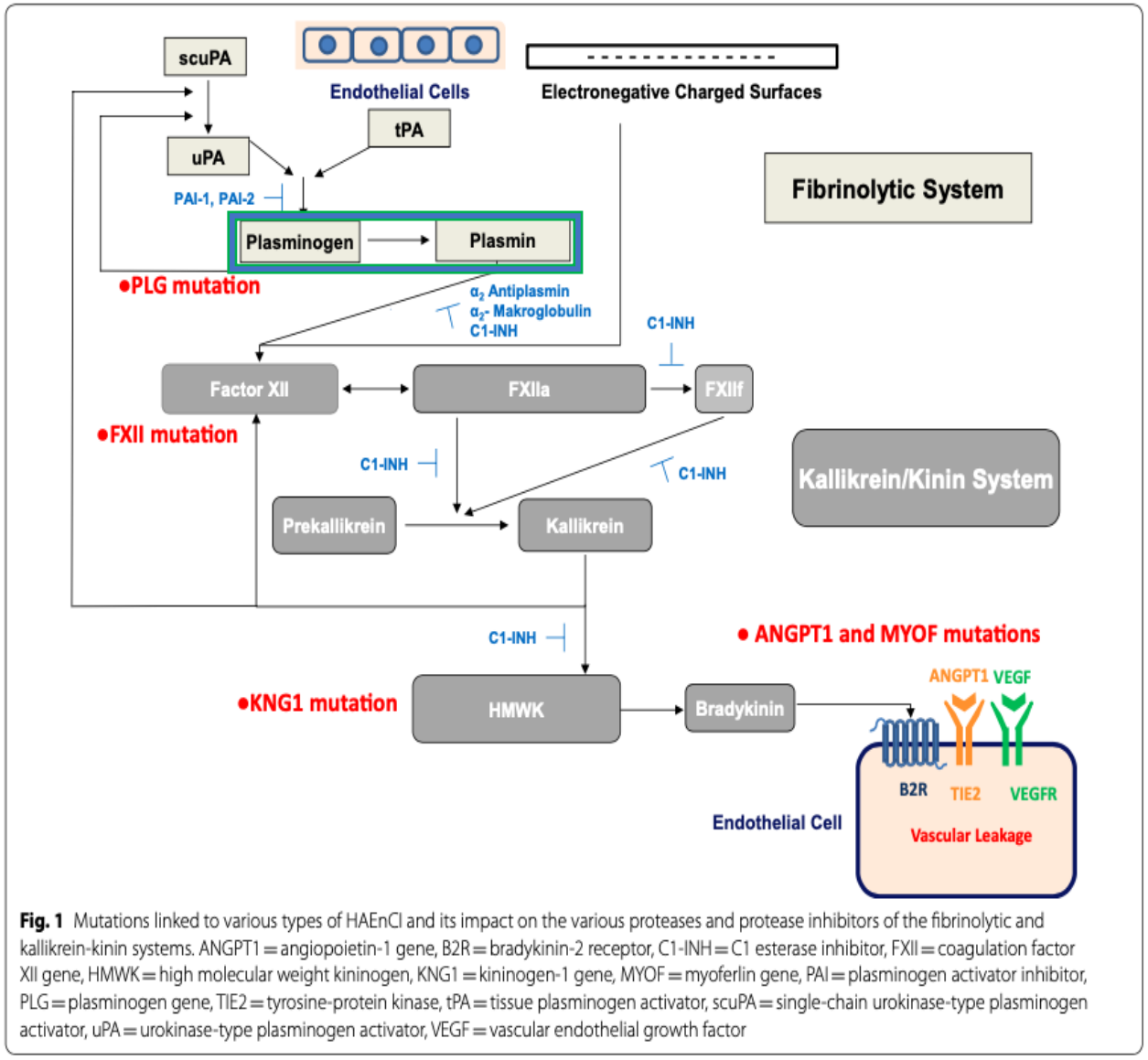


Fig. 1 Mutations linked to various types of HAEnCI and its impact on the various proteases and protease inhibitors of the fibrinolytic and kallikrein-kinin systems. ANGPT1 = angiopoietin-1 gene, B2R = bradykinin-2 receptor, C1-INH = C1 esterase inhibitor, FXII = coagulation factor XII gene, HMWK = high molecular weight kininogen, KNG1 = kininogen-1 gene, MYOF = myoferlin gene, PAI = plasminogen activator inhibitor, PLG = plasminogen gene, TIE2 = tyrosine-protein kinase, tPA = tissue plasminogen activator, scuPA = single-chain urokinase-type plasminogen activator, uPA = urokinase-type plasminogen activator, VEGF = vascular endothelial growth factor

- AD GOF missense mutation in exon 9 of *PLG*, c.988A>G; (p.Lys330Glu)
- 146 patients from 33 families
- Present usually in adulthood as compared to paediatric in C1-INH deficiency HAE

- High - tongue, face, laryngeal oedema
- low - peripheral or abdominal or genital swelling

- ACE inhibitors tend to precipitate attacks

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