



BME462

RESEARCH TECHNIQUES

Antimicrobial Host Defence Peptides: Functions and Clinical Potential

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Kübranur Öner
15290168

Aylin Mustafa
15290637

Işıl Yazgan
15290190

What are the Cationic Host Defense Peptides (CHDP) ?

- Natural peptides
- Can combat infections through their direct microbicidal properties and/or by influencing the host's immune responses.
- Known as antimicrobial peptides

Why CHDPs are Needed ?

- For use in antibiotic-like treatments due to;
 - i. increase in multidrug-resistant pathogens
 - ii. decline in the discovery of new antibiotics in infection control.
- For develop an alternative strategies for;
 - i. both kill pathogens and resolve harmful inflammation.

Structure Properties and Conformation Groups of CHDP

- Typically amphipathic small peptides.
- Have fewer than 50 amino acids.
- Have a net positive charge of +2 to +9 at physiological pH.
- They are classified into four structural groups according to the basis of their conformation.
 - i. α - helical linear peptides
 - ii. Peptides with β - sheet with disulfide bridges
 - iii. Cyclic peptides
 - iv. Peptides with extended flexible loop structures

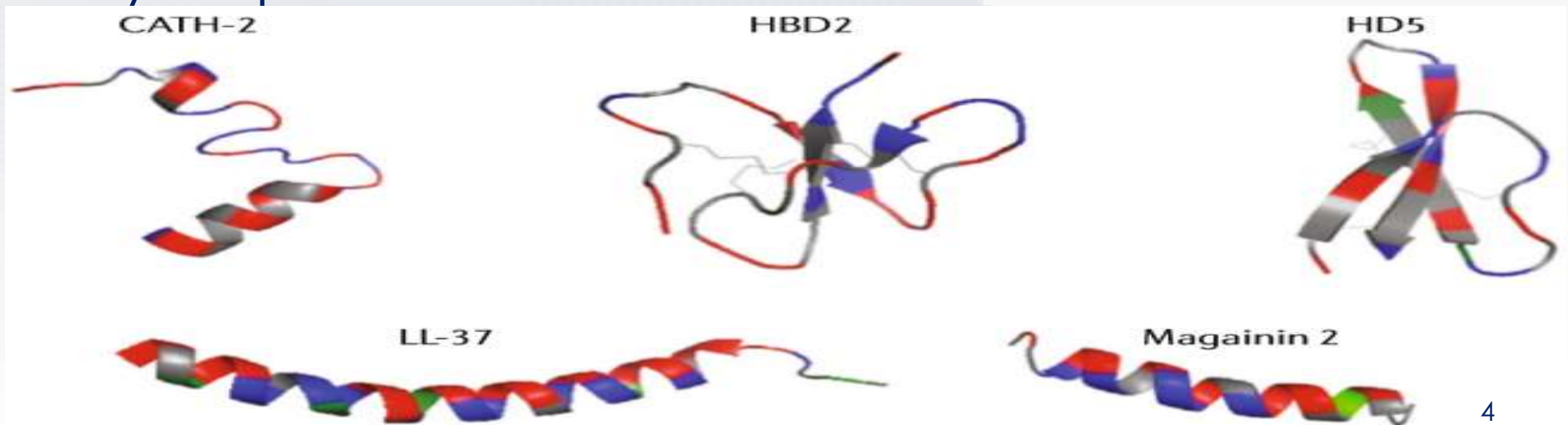
Sources of CHDPs

1. Naturally Occurring CHDP

There are more than 2,600 natural antimicrobial peptides.

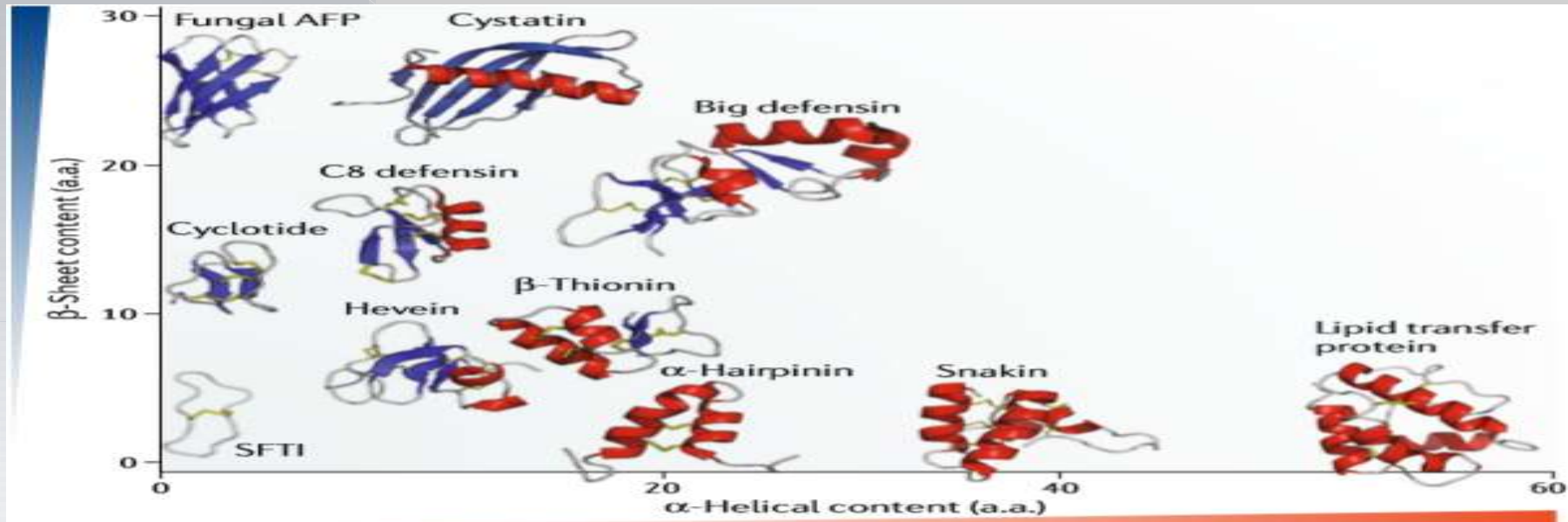
i. Vertebrate CHDP

- ⦿ Amphipathic peptides
- ⦿ Contain amino acids with hydrophilic and hydrophobic side chains



ii. Invertebrate, Plant and Fungal CHDP

- Similar to those from vertebrates
- Small amphipathic peptides with an overall positive net charge.



2. Synthetic Peptides Derived from CHDP

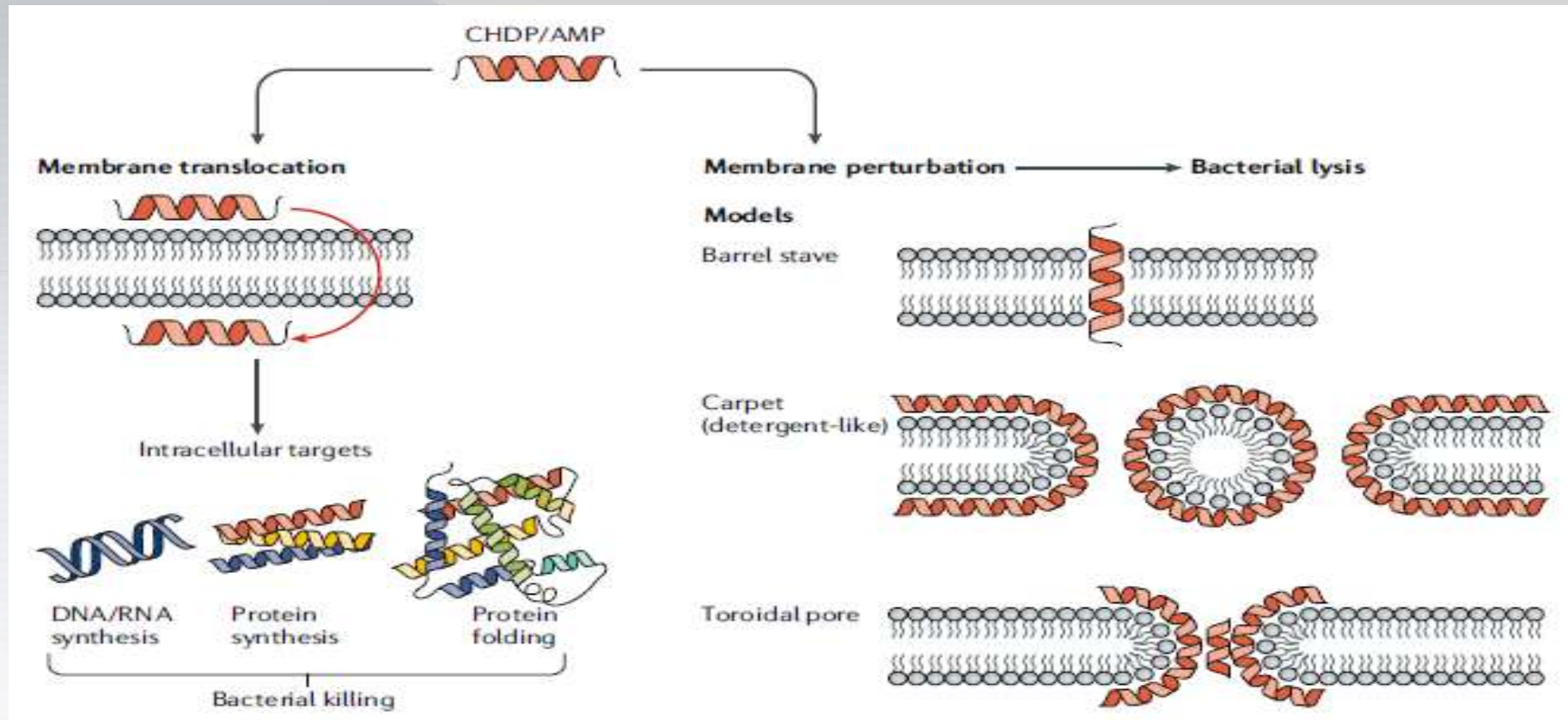
For example ; innate defence regulator peptides (IDRpeptides);

- Such small synthetic cationic peptides derived from natural CHDP.
- Can control infection in vivo and reduce inflammation.

Mechanism of Action

1. Antimicrobial Action

1.1 Antibacterial Activities



- The bacterial membrane is the main target for most cationic peptides.

1.2 Antiviral Activities

Influenza virus	HNP	Virus aggregation; inhibition of PKC disrupts IAV endosomal trafficking; enhanced neutrophil phagocytosis of IAV
HIV	HNP	Disruption of cellular entry; inhibition of PKC activity, interfering with HIV replication
Adenovirus	α -Defensins	Peptide binding to adenoviral capsid prevents uncoating and nuclear entry of the viral genome; dependent on optimal peptide hydrophobicity and charge

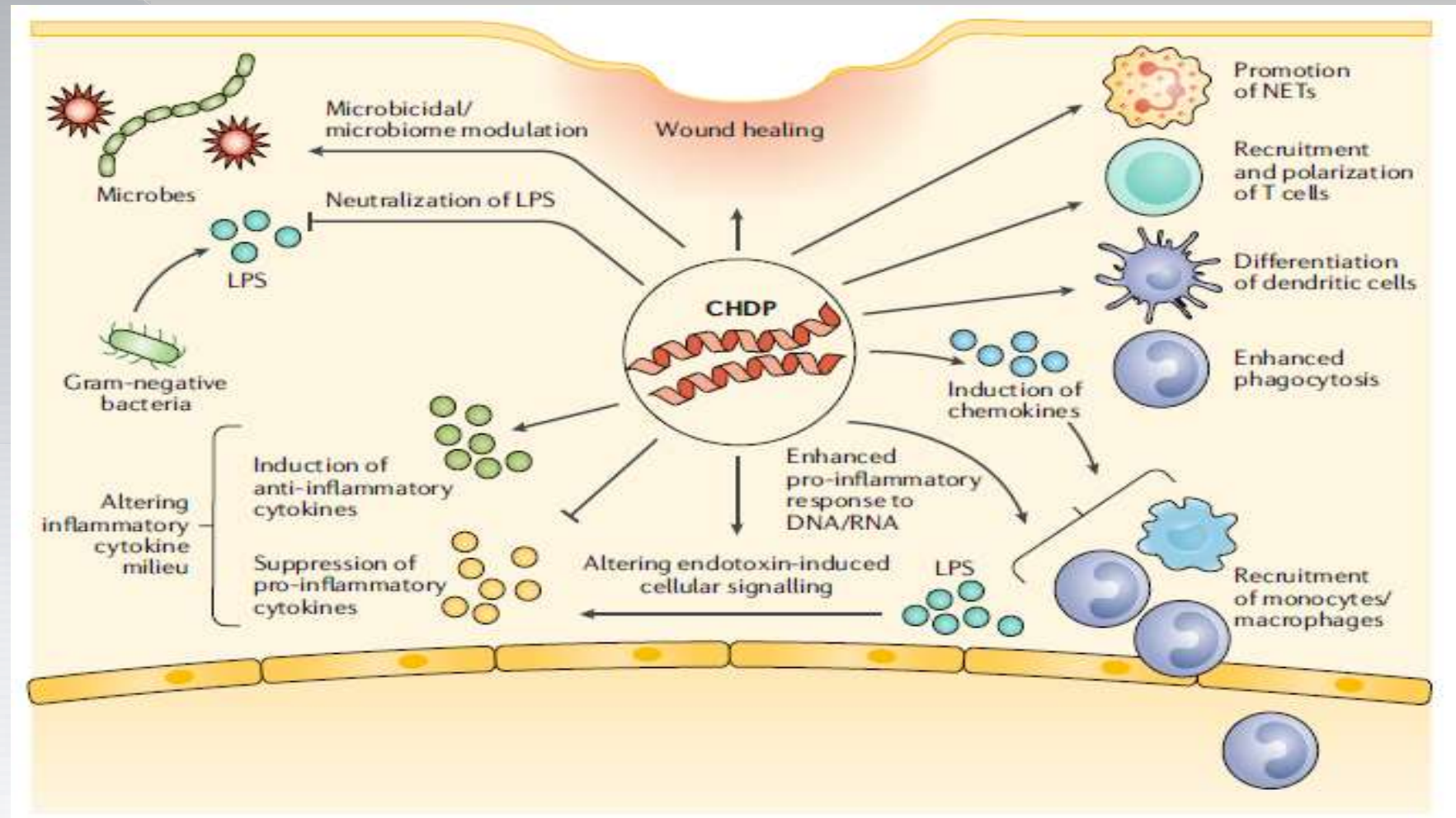
CHDP destabilizes the viral envelope by;

- damaging the virions
- inhibiting infectivity
- decreasing viral replication
- binding to cellular receptors

1.3 Antifungal Activities

- ⦿ Mechanisms of CHDP ranging from effects on mitochondrial functions to membrane effects.
- ⦿ Fungal biofilms are highly resistant to antifungals. It is thus important to screen newly developed CHDP- based antifungals.

2. Immunomodulatory Actions



- Protective activation of the innate immune is one of the key mechanisms underpinning the ability of CHDPs to promote early clearance of infections.

CHDP-Based Therapies

□ Antimicrobial Therapies

i. Preclinical Studies:

- CHDP may be immobilized on the surfaces of biomaterials to prevent adhesion of bacteria.
- First-line antiviral treatments for use during pandemics or for viral infections for which vaccines are not available.



ii. Clinical Trials

- LL-37 for venous leg ulcers
- Dalbavancin for acute bacterial skin infections
- PAC-113 for oral candidiasis

□ Immunomodulatory Therapies

i. Preclinical Studies:

- LL-37 prevented the development of arthritis and cartilage degradation of the joints.
- IDR peptides are applied as adjuvants for new vaccine formulations.
- CHDP in wound healing is also being explored. Growth factors associated with stimulation of regeneration of tissues induce the production of endogenous CHDP.



ii. Clinical Trials

- Use of silicone hydrogel contact lenses coated with a synthetic immunomodulatory peptide
- The human cathelicidin LL-37 has been applied to enhance healing of hard-to-heal venous leg ulcers.



Limitations and Solutions

Limitations:

- ❖ High cytotoxicity
- ❖ High production cost
- ❖ Peptide stability

Solutions:

- ❖ Shorter synthetic peptides have demonstrated negligible toxicity and no immunogenicity.
- ❖ New production methods such as the efficient use of expression systems reduce the costs of production.
- ❖ -D-amino acid peptides can be used.
 - Modification of peptides by amidation or acetylation of the terminal regions can be done.

Conclusions

- Although, research in this field was initially focused on the development of new 'antibiotics' based on cationic antimicrobial peptides, it is now well appreciated that CHDP have a critical role in immunity.
- Despite many associated challenges and the limited understanding of structure–function relationships, the potential of CHDP- based therapies remains a promising new clinical direction.

THANK YOU !