In situ mechanistic insight to antibacterial action of membrane-incising β-peptide lamellae

https://doi.org/10.17952/37EPS.2024.P1085

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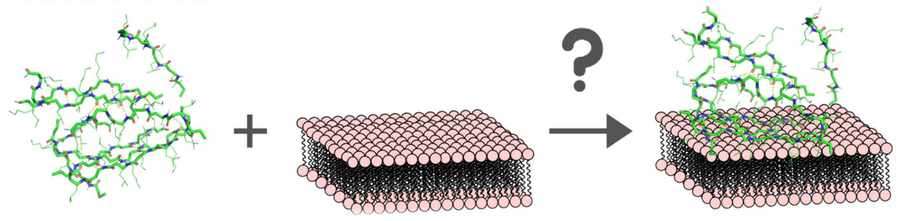
Introduction

β[3]-peptides exhibit:
- Resistance against protease degradation
- Unique folding architecture
- Therapeutic applications (delivery systems, bionanomaterials)

Our short cationic β[3]-peptides:
- Non-natural β[3]-amino acids
- Amino acids with alternating R and S chirality
- Rich in hydrophobic residues (Leu)
- Several positively charged residues (Lys)

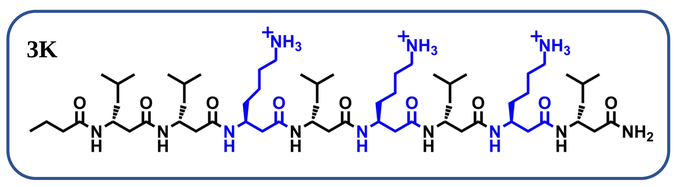
Main goals

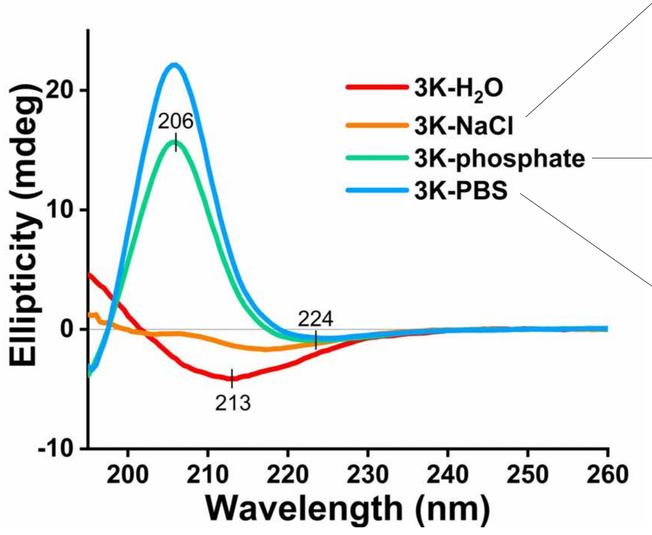
- Exploit the **self-assembly** capacity in various conditions
- Characterize **membrane activity**
- Study interactions with biologically relevant phosphate agents
- Test their antibacterial effect

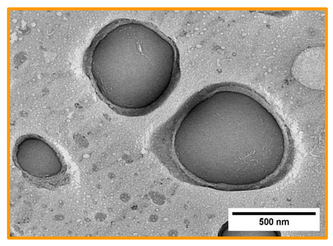


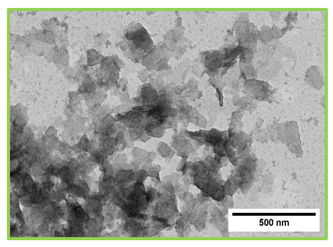
Results

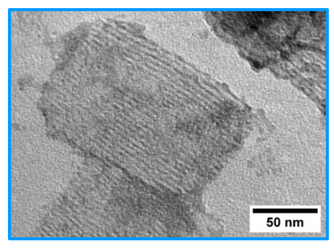
Previous Results - Structure and assembly manipulated by environmental parameters

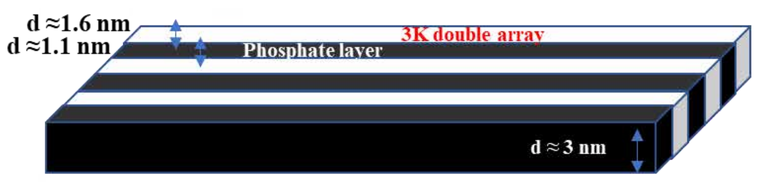


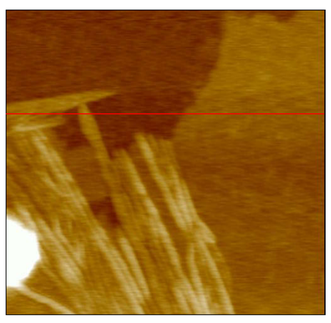


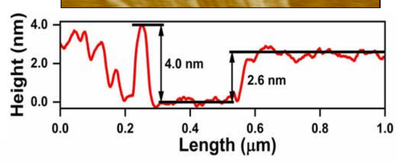




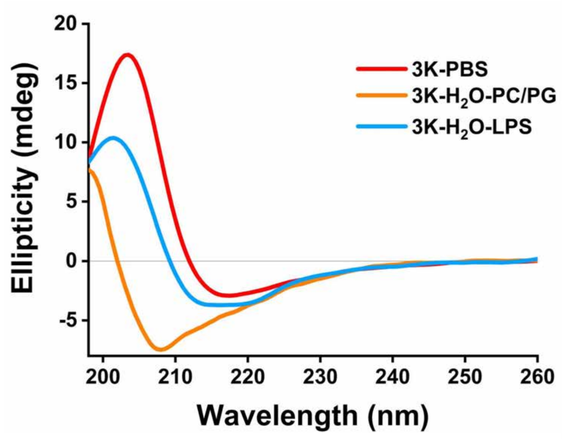


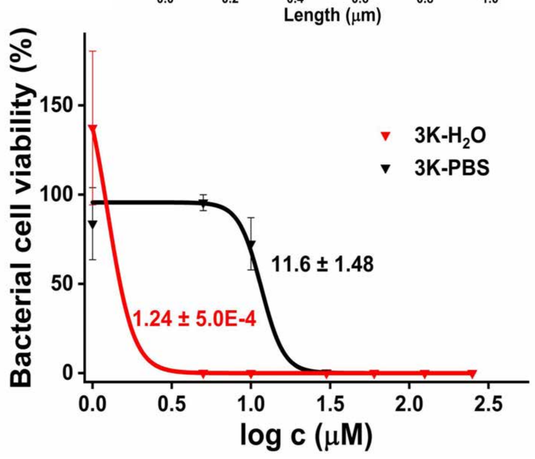






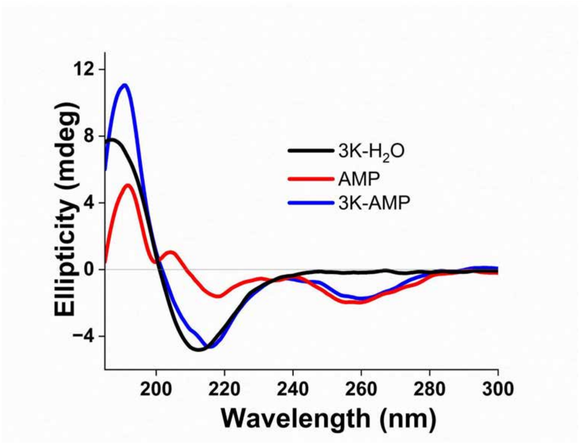
- Double arrays of 3K in parallel orientation, where intermolecular H-bonds stabilized the assembly while the two arrays formed a hydrophobic core composed of the leucine side chains.
- Several double arrays of 3K are connected by a narrow layer of phosphate ions that coordinate lysine side chains.
- The zig-zag 3K molecules span ~ 3.1 nm, whereas the width of the double 3K arrays and the hydrophilic lysine-phosphate region is approximated to be 1.8 nm and 1.1 nm, respectively.

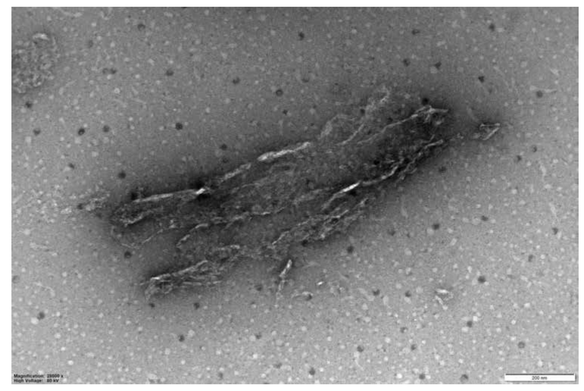




Interactions with biologically relevant phosphate agents

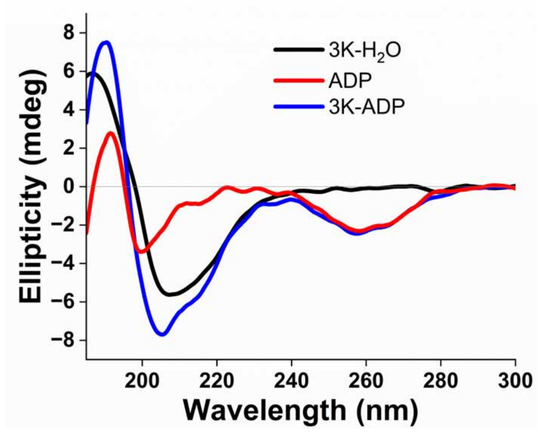
3K:AMP (1:4)

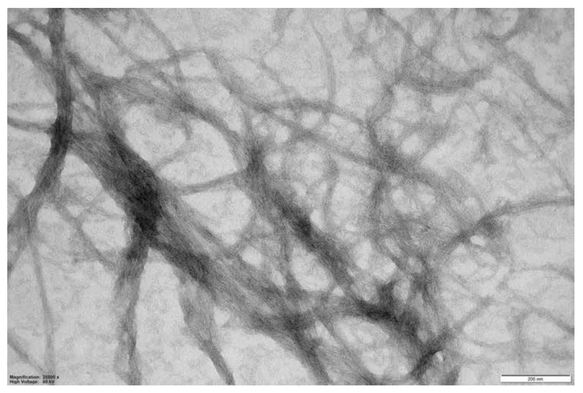




Less packed and more disperse objects

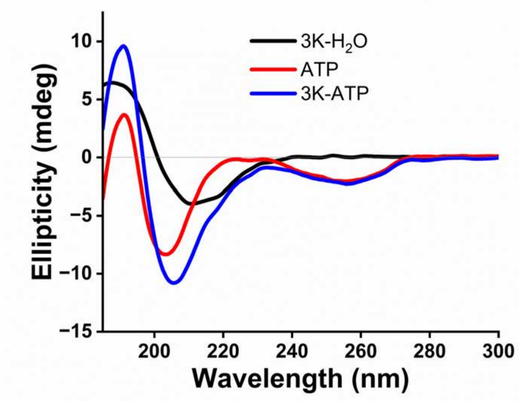
3K:ADP (1:4)

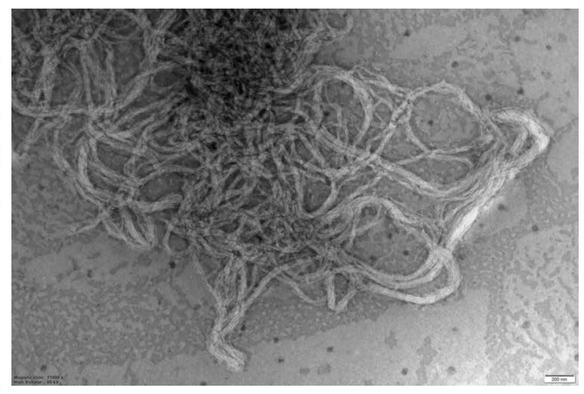




Similar sub-unit packing as 3K-PBS
→ long fibril-like thread morphologies

3K:ATP (1:4)





Similar sub-unit packing as 3K-PBS
→ infinite fibril-like thread morphologies

Conclusion

- Short cationic/hydrophobic β[3]-peptides can effectively self-assemble to associate with various morphologies depending on the conditions.
- Previously, we exploited the environmental sensitivity of 3K in various environments → 3K in PBS resulted in high antibacterial efficacy and low cytotoxicity.
- Triggered by these observations, we studied the interactions of various other phosphate moieties with 3K.
- Initial results from CD and TEM suggest that the different oligophosphates contribute effectively to the co-assembly formation resulting in unique morphologies.
- Similar to biological filaments, such as actin and amyloids, fibrillar morphologies are observed which appear to be continuous and infinite. The length of these fibrils are influenced by the number of phosphates.
- Owing to their unique morphologies, these fibrils could potentially act as peptide nanonets to inhibit the bacterial growth on specific sites in the human body.

References

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Acknowledgements

This work was funded by the Ministry of Innovation and Technology of Hungary from the National Research, Development and Innovation Fund, financed under the TKP2021-EGA-31 and the 2020-1-1-2-PIACI-KFI_2020-00021, KKP_22 144180, funding schemes. Support from Eötvös Loránd Research Network, grant n.o. SA-87/2021, is also acknowledged.