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MDPI

MD Simulations Reveal the Structural Mechanisms Behind the Divergent Cytotoxicity of a Bacterial Amyloid Peptide

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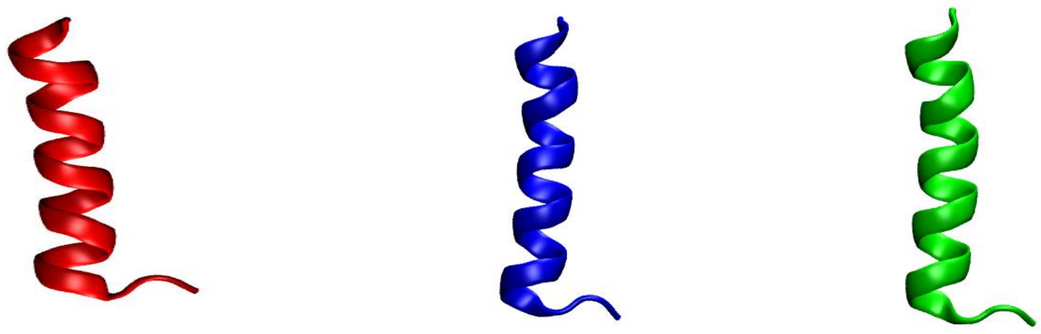
INTRODUCTION & AIM

PSMα3 is a 22-residue amphipathic peptide known for its involvement in biofilm formation a (**MEFVAKLFKFFKDLLGKFLGNN)** and potent cytotoxic activity. Because of its biological significance, it has become an important target for structural and mechanistic studies.Experimental work by Fligelman et al. (2019) (https://doi.org/10.1016/j.str.2019.12.006) demonstrated that specific point mutations can markedly alter the peptide's structural stability and functional behavior. In particular, the **Lys17→Ala** mutation leads to a substantial decrease in α-helical content and a strong reduction in cytotoxicity relative to the wild-type (WT) peptide.Conversely, the **Asp13→Ala** mutation also diminishes α-helicity but unexpectedly increases cytotoxicity compared to WT. This suggests that Asp13 may regulate membrane interactions—possibly by influencing local charge distribution, aggregation propensity, or binding affinity. The objective of this study was therefore to employ molecular dynamics (MD) simulations to elucidate how these mutations reshape the conformational landscape of PSMα3 and to provide mechanistic insight into their experimentally observed effects.

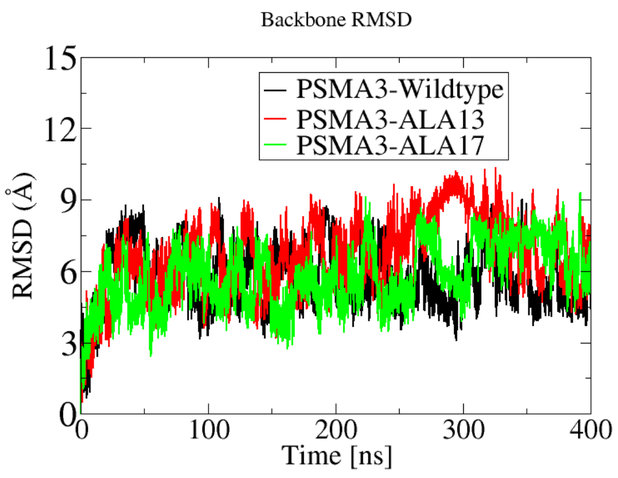
METHOD

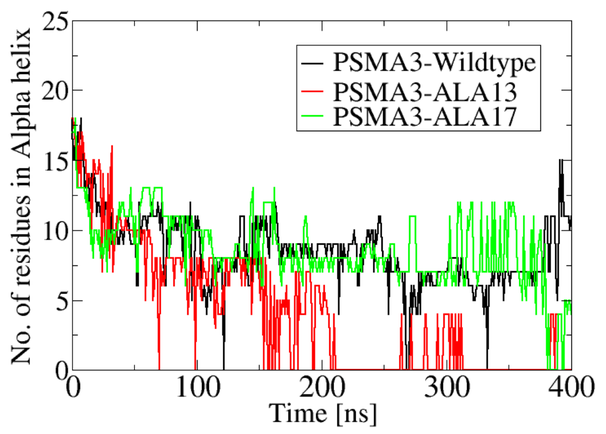


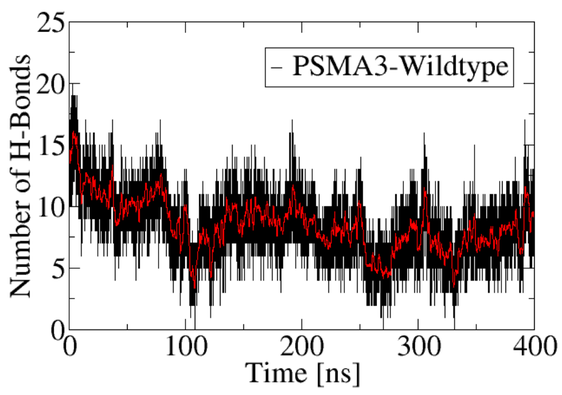
PSMα3-Wildype **PSMα3-Ala13** **PSMα3-Ala17**

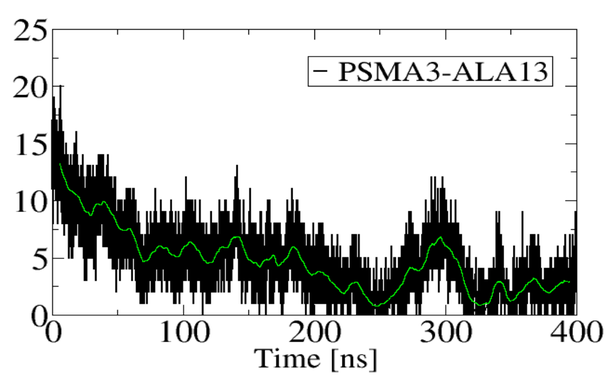
All molecular dynamics (MD) simulations were carried out using the CHARMM36m force field in explicit TIP3P water. Each system (WT, D13A, and K17A) was simulated through 20 independent replicas of 200 ns to ensure broad sampling of the conformational space. In addition, a well-tempered metadynamics simulation was performed for each system to enhance sampling of key conformational transitions and capture slow structural rearrangements.

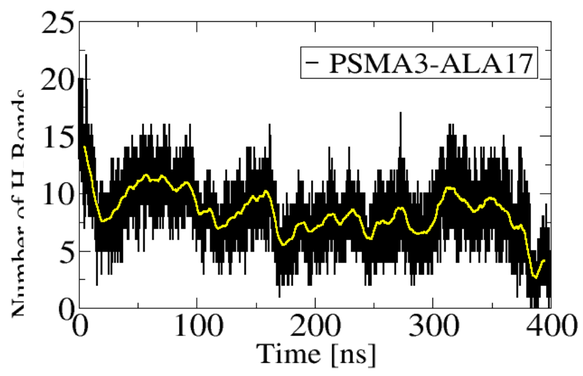
RESULTS & DISCUSSION

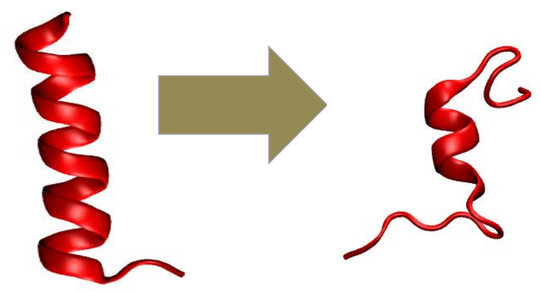




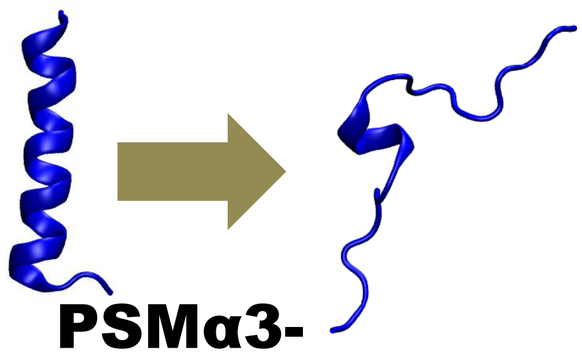








PSMα3-Ala17



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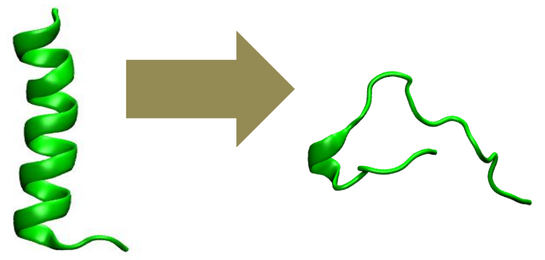

PSMα3-Ala17

CONCLUSION

The enhanced cytotoxicity of the Asp13 → Ala mutant, despite its reduced α-helicity, indicates that cytotoxic activity is not solely determined by secondary structure. This paradox suggests that the specific mode of peptide-membrane interaction is a critical factor governing its toxic function.

ACKNOWLEDGEMENT

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