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Extreme Amyloid Polymorphism in *Staphylococcus aureus* Virulent PSMα Peptides

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Amyloids are structured protein fibrils associated with human fatal neurodegenerative diseases. Recently, microbial amyloids were found to be ubiquitous across kingdoms of life and to perform many physiological functions, including as key virulence determinants in microbes. These activities include stabilizing microbial biofilms, mediating host-pathogen interactions and competing with other bacteria. In this study we shed light on the functional and structural roles of amyloid-forming peptides called Phenol Soluble Modulins (PSMs) secreted by the pathogenic *Staphylococcus aureus*. As a means of pathogenesis, PSMs cause lysis of human cells including leukocytes and erythrocytes, stimulate inflammatory responses and contribute to biofilm development particularly in virulent *S. aureus* strains such as the community-associated methicillin-resistant *S. aureus* (CA-MRSA). We found that PSMα1 and PSMα4, involved in biofilm structuring, form cross-β amyloid fibrils that were linked with eukaryotic amyloid pathologies, shown here for the first time at atomic resolution in bacteria. These fibrils confer high stability to the biofilm. In contrast, the cytotoxic activity of PSMα3 against human cells stems from the formation of cross-α fibrils (Tayeb-Fligelman *et. al.*, *Science* 2017) that are at variance with the cross-β fibrils. Interestingly, a truncated PSMα3, which forms reversible fibrils and has antibacterial activity, reveals two polymorphic and a typical β-rich fibril architectures, both radically different from both the cross-α fibrils formed by full-length PSMα3 and from the cross-β fibrils formed by PSMα1 and PSMα4 (Salinas *et. al.*, *Nature Communications*, *in press*). Our results point to structural plasticity being at the basis of functional diversity exhibited by S. aureus PSMαs.

Biography:

Nir Salinas is a doctoral student in the Structure Function Relationships in Microbial Functional Amyloids' lab, faculty of biology at the Technion-Israel Institute of Technology, under the supervision of Assist. Prof. Meytal Landau. Nir Salinas Ph.D. studies determine the fascinating and unexplored structures of bacterial functional amyloids, correlate the structures to their functions as key virulence determinants, and device means for their regulation. The ultimate goal of Nir Salinas research is to develop novel antivirulence and antibacterial drugs with a new mechanism of action based on Amyloidogenic peptides.