Extreme Amyloid Polymorphism in *Staphylococcus aureus* Virulent PSMα Peptides

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Abstract

The mechanisms of amyloid protein assembly into fibrous structures have been studied for decades, particularly since amyloids are associated with neurodegenerative and systemic human diseases. In contrast, functional amyloids that participate in dedicated physiological activities in all kingdoms of life were poorly characterized and their importance to human health is only starting to emerge. Functional amyloids were discovered mostly in microbes, serving as key virulence factors and thus present novel targets for antimicrobial agents. The structural hallmarks of functional amyloids – if any – and how they can be distinguished from disease-associated amyloids remain unclear. We investigated the structure-function-fibrillation relationships of microbial functional amyloids, their interactions with host amyloids and receptors and explore routes to modulate their activities. By leveraging unique methodologies of X-ray microcrystallography, we were the first to obtain atomic structures of bacterial functional amyloids. We discovered that two peptides, PSMα1 and PSMα4, involved in biofilm structuring of the pathogenic bacterium *Staphylococcus aureus*, form cross-β amyloid fibrils linked with eukaryotic amyloid pathologies, shown here for the first time at atomic resolution in bacteria (Salinas *et. al.*, *Nature Communications* 2018). These fibrils confer ultra-stability to the biofilm. We also revealed unique amyloid-like structures in the *S. aureus* PSM peptide family, including, to our surprise, a structure of a cross-alpha amyloid-like fibril exposing surprising departure from pathological amyloids in which β-rich structures are central. The fibrils, of the full-length PSMα3 peptide, are toxic to human cells, clarifying their involvement in pathogenicity (Tayeb-Fligelman et. al., *Science* 2017). Interestingly, a truncated PSMα3, which forms reversible fibrils and has antibacterial activity, revealed two polymorphic and atypical 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* 2018). Our results point to structural plasticity being at the basis of functional diversity exhibited by *S. aureus* PSMαs.