Functional Protein Fibrils

Meytal Landau¹, Einav Tayeb-Fligelman¹, Nir Salinas¹, Sergei Perov¹, Ofir Lidor¹, Itzik Engelberg¹, Nimrod Golan¹

¹ Department of Biology, Technion – Israel Institute of Technology, Haifa, Israel
mlandau@technion.ac.il

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 unique amyloid-like structures, including, to our surprise, a structure of a full-length bacterial cross-alpha amyloid-like fibril revealing surprising departure from pathological amyloids in which beta-rich structures are central. The fibrils, of the PSMα3 peptide secreted by the pathogenic bacterium Staphylococcus aureus, are toxic to human cells, clarifying their involvement in pathogenicity. In contrast, amyloidogenic peptides involved in biofilm structuring share similar atomic structures with pathological amyloids, forming ultra stable cross-beta structures that stabilize the biofilm matrix. Surprisingly, three fibrillating antibacterial peptides secreted by different organisms (bacteria, amphibian and human) exposed extremely polymorphic fibrous architectures, all markedly different from the cross-beta fibril. Given our results we predict that the structural and functional repertoire of functional amyloids is far more diverse than previously anticipated, providing a rich source of targets for antimicrobial drug discovery.

Figure

Figure 1. Highly polymorphic amyloid fibril structures of S. aureus PSMα peptides.

References