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Journal Club

PROTEIN AGGREGATION

AMYLOIDS AS KINASE SIGNALLING PLATFORMS

Amyloids are the best-known higher-order protein structures, forming distinct rigid fibrils. They were originally defined as a unique form of protein folding disorder, which leads to unspecific cellular dysfunction in many diseases, in particular neurodegenerative disorders. Ironically, these 'disordered' protein aggregates feature a central cross-β spine, with solvent-excluded, self-complementing steric zipper interactions, thereby sharing the core characteristics of 'highly ordered' cross-β-sheet packing. Is the beauty of these rigid fibrils merely awry bug of nature? Intriguingly, amyloids were also found to contribute to signal transduction in human. In 2012, Li et al. revealed the amyloidal nature of a class of cytosolic RHIM-containing kinases, RIPK1 and RIPK3. With this discovery, a novel amyloidal kinase-mediated signalling transduction rose into view.

It has long been observed that inside cells RIPK3 assembles into nontoxic punctae of unknown biophysical properties. Li et al. found that these RIPK3-contaning punctae, as well as equivalent RIPK1 punctae, represent the classic β-amyloids. Most importantly, they found that the RIPK1/RIPK3-amyloids play an essential role in necroptosis signal transduction, specifically via recruiting and phosphorylating a membrane-damaging protein MLKL.

An important question soon emerged: what's the purpose for RHIM kinases to form rigid fibrils? Firstly, this ultra-stable atomic structure helps to maintain the kinase activation status of RIPKs, preventing degradation or inactivation. Further, during necroptosis, the inter-filament interactions in RIPK amyloids increase to form a large, branched fibrillar network. We infer that this unique highly ordered RHIM amyloid may represent a special form of kinase working pattern: the 'intensity' of the kinase signal heaps up along the fibrillation process, while the signal is sustained as the delicate fibril network grows.

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Meanwhile, it cannot be ignored that signal transduction is a temporal process; that said, any signal hub should not be permanently assembled. Indeed, washing out the necroptosis-inducer brings the cell fate back to survival. This provokes a question: without the artificial harsh conditions allowing to break up the amyloid fibrils, when and how do the RHIM-amyloids get reversed in the cellular context? The tipping point of the assembly and the disassembly process of RIPK1/RIPK3-amyloid would set the fundamental difference distinguishing the functional amyloid from those disease-related amyloidal aggregates. Finding the key to untangle these functional amyloids in the cell is perhaps the most challenging task to follow on the discovery of functional RHIM-amyloids by Li et al.

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ORIGINAL ARTICLE Li, J. et al. The RIP1/RIP3 necrosome forms a functional amyloid signaling complex required for programmed necrosis. *Cell* **150**, 339–350 (2012)