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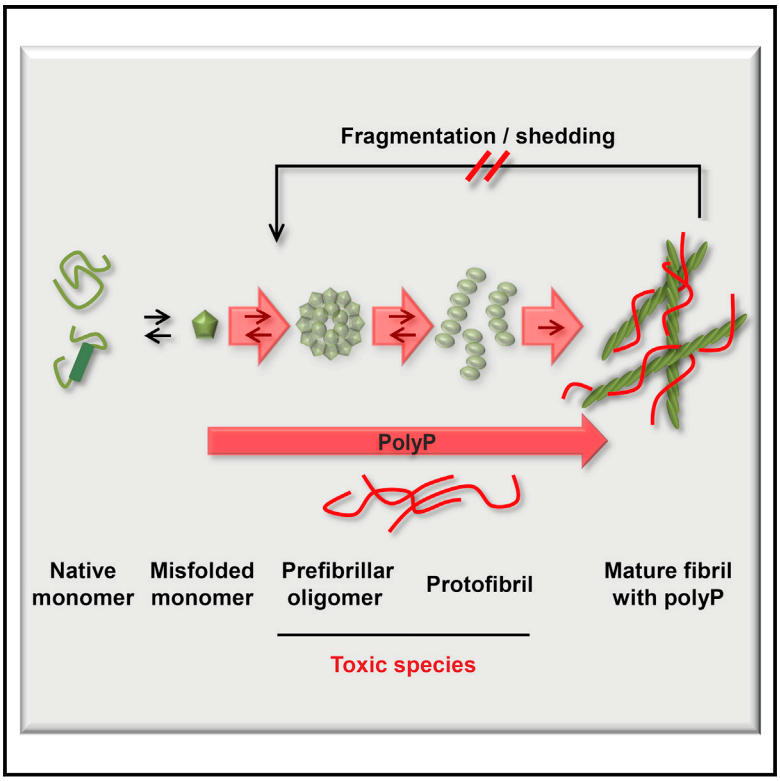
Molecular Cell

Polyphosphate: A Conserved Modifier of Amyloidogenic Processes

Graphical Abstract



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In Brief

Polyphosphate has been around since prebiotic times. Cremers et al. now demonstrate that this universal polymer serves as scaffold for amyloidogenic proteins, effectively nucleating fibril formation. polyP's influence on fibril formation and stability has wide-reaching consequences, from increasing biofilm formation in pathogenic bacteria to reducing amyloid cytotoxicity in disease models.

Highlights

- Polyphosphate accelerates amyloid fibril formation in pro- and eukaryotes
- Polyphosphate alters morphology, seeding capacity, and stability of amyloid fibrils
- Polyphosphate stimulates amyloid-dependent biofilm formation in bacteria
- Polyphosphate mitigates amyloid toxicity in disease models

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Polyphosphate: A Conserved Modifier of Amyloidogenic Processes

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SUMMARY

Polyphosphate (polyP), a several billion-year-old biopolymer, is produced in every cell, tissue, and organism studied. Structurally extremely simple, polyP consists of long chains of covalently linked inorganic phosphate groups. We report here the surprising discovery that polyP shows a remarkable efficacy in accelerating amyloid fibril formation. We found that polyP serves as an effective nucleation source for various different amyloid proteins, ranging from bacterial CsgA to human α-synuclein, $A\beta_{1-40/42}$, and Tau. polyP-associated α-synuclein fibrils show distinct differences in seeding behavior, morphology, and fibril stability compared with fibrils formed in the absence of polyP. In vivo, the amyloid-stimulating and fibril-stabilizing effects of polyP have wide-reaching consequences, increasing the rate of biofilm formation in pathogenic bacteria and mitigating amyloid toxicity in differentiated neuroblastoma cells and *C. elegans* strains that serve as models for human folding diseases. These results suggest that we have discovered a conserved cytoprotective modifier of amyloidogenic processes.

INTRODUCTION

Formation of insoluble protein fibrils plays a crucial role in many different processes, ranging from bacterial biofilm formation to human folding diseases, including Alzheimer's and Parkinson's disease (Galvin et al., 2001; Hufnagel et al., 2013; Selkoe, 2001). The amyloidogenic proteins that are involved in these processes have little in common apart from their ability to convert from soluble proteins into insoluble cross-β-sheet-rich fibrils (Eichner and Radford, 2011). The rate-limiting step in amyloid fibril formation appears to be the initial nucleation step, when monomeric peptides or proteins adopt a β sheet-rich, nucleation-prone conformation. Other monomers are then converted into this conformation, eventually culminating in the formation of fibrils, which are deposited in either the intra- or extracellular space. The observed cytotoxic and neurological effects that accompany disease amyloid fibril formation appear to be less due to the final products but due to the accumulation of toxic oligomers that are transiently present prior to the formation of mature amyloid fibrils or generated by the shedding off of mature fibrils (Chen et al., 2015). The toxicity of these oligomers may arise from their ability to increase membrane permeability, affect mitochondrial function, and/or alter the cytoskeleton (Roberts and Brown, 2015). Therapeutic measures targeting amyloid-related protein folding diseases currently under investigation focus primarily on stabilizing nontoxic early intermediates (Hefti et al., 2013). However, acceleration and stabilization of the fibril-forming process should also act to mitigate toxicity by reducing the accumulation of toxic oligomers. This idea is consistent with reports of amyloid fibril depositions in patients with no discernable cerebral degeneration (Ingelsson et al., 2004). Therefore, it appears that amyloids can polymerize in situ without eliciting cellular toxicity.

Polyphosphate (polyP), which consists of up to 1,000 phosphoanhydride bond-linked phosphate monomers, has been found in all prokaryotic and eukaryotic organisms studied so far (Kumble and Kornberg, 1995; Rao et al., 2009). Present in the cytosol and most major organelles, polyP has also been shown to be secreted into the extracellular space by platelets, astrocytes, and bacteria (Holmström et al., 2013; Müller et al., 2009; Sakatani et al., 2016). polyP is known for its general stress protective functions and has been recognized for specific roles in virulence, biofilm formation, and blood clotting (Morrissey, 2012; Rao et al., 2009). Yet, despite the universal presence and highly conserved nature of polyP, the mechanism(s) by which this simply structured polymer affects these diverse processes has remained largely enigmatic. Recent work from our lab revealed that polyP stabilizes unfolding proteins, thereby protecting bacteria against stress conditions that cause widespread protein unfolding and aggregation (Gray et al., 2014). In vitro studies revealed the surprising result that low micromolar concentrations of polyP-chains effectively convert various thermolabile, mainly α-helical proteins into thermostable β sheet-rich intermediates (Gray et al., 2014) (Figures S1A and S1B).