**Polyphosphate is a primordial chaperone.**


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**Recommendations:**

- Very Good

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This elegant work reveals a novel role of polyphosphate as a chemical chaperone protecting bacterial cells from oxidative and other stresses. Polyphosphate is a linear polymer of a few to many hundreds of phosphate (Pi) residues linked by high-energy phosphoanhydride bonds. This ubiquitous polymer is found in bacteria, protists, and mammalian cells, and it was likely present prebiotically [1]. Recent work demonstrated that polyphosphate was able to suppress thermal aggregation of the enzyme glyceraldehyde 3-phosphate dehydrogenase without loss in the enzymatic activity [2], and the present work confirms these results using luciferase and citrate synthase. The authors also demonstrate, using mutants deficient in polyphosphate kinase or exopolyphosphatase, that this protection also occurs in live bacteria.

**References**

1. Polyphosphate and its diverse functions in host cells and pathogens.
   PMID: 23658515 DOI: 10.1371/journal.ppat.1003230

2. Effect of poly(phosphate) anions on glyceraldehyde-3-phosphate dehydrogenase structure and thermal aggregation: comparison with influence of poly(sulfoanions).
   PMID: 23811344 DOI: 10.1016/j.bbagen.2013.06.024

**Disclosures**

None declared

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At least two long known but puzzling phenomena – i) that, in all organisms analysed so far, cellular ATP levels go down upon oxidative treatment and ii) that bacterial polyphosphate kinase (PPK) mutants are hypersensitive to various stresses – are explained by a recent study by Gray et al. establishing inorganic polyphosphate as an ubiquitous and general protein chaperone. Regarding ATP levels, it appears that, at least in E. coli, a rapid drop to below 50% of the normal concentration observed in response to the proteotoxic oxidant HOCl is minimised in ppk knock-out cells. This suggests that, upon oxidative stress, a substantial fraction of cellular ATP is diverted to the synthesis of polyphosphate, an isoenergetic and reversible reaction catalysed in both directions by PPK. A large part of the study is dedicated to demonstrating that the polyphosphate levels thus achieved (about 50mM) are sufficient to confer protection from aggregation both globally and to specific model protein substrates. Polyphosphate turned out to be effective in vitro also not only against oxidative agents, but also other stressors, suggesting it acts directly on client proteins and not by neutralising a particular stress type, as is indeed seen in vitro assays. Interestingly, already with 2mM polyphosphate almost no aggregated proteins were observed in an experiment in which soluble and insoluble fractions of the E. coli lysate before and after heat shock were examined by SDS-PAGE. This, one could add, makes polyphosphate an interesting additive for recombinant production of aggregation-prone proteins. The fact that this inorganic polymer is already effective at mM and, in the case of some substrates, even nM concentrations, suggests it differs from chemical chaperones (osmolytes), which stabilise proteins indirectly by interacting with the solvent, and functions more like protein chaperones. In an assay in which luciferase was denatured in the absence and presence of polyphosphate, it was demonstrated that, while the substrate loses its activity in both cases, it can be later reactivated by the ATP-dependent chaperone system DnaK-DnaJ-GrpE if protected by polyphosphate. This observation leads to a fascinating, although still largely speculative, model. Upon oxidative stress, ATP levels go down and polyphosphate is produced, preventing protein aggregation in a holdase-like fashion. Due to the low ATP levels, active ATP-dependent refolding is down-regulated, as it would be anyway – as long as the stress is still present – leading to a futile unfolding-refolding cycle. Upon relief of stress conditions, ATP is recovered from polyphosphate and unfolded proteins, now released, can be refolded by the ATP-dependent molecular machines. Many questions remain to be answered. Does polyphosphate, long known to be a ubiquitous cellular component, have the same role in other organisms, including humans? What is the mechanism of its action? One can think of many others. However, the number of questions that now come to mind is a proof that the study by Gray et al. truly changes the way we think of protein quality control.

Disclosures
None declared

Abstract:

Abstract

Composed of up to 1,000 phospho-anhydride bond-linked phosphate monomers, inorganic polyphosphate (polyP) is one of the most ancient, conserved, and enigmatic molecules in biology. Here we demonstrate that polyP functions as a hitherto unrecognized chaperone. We show that polyP stabilizes proteins in vivo, diminishes the need for aggregation-prone proteins, now released, can be refolded by the ATP-dependent molecular machines. Many questions remain to be answered. Does polyphosphate, long known to be a ubiquitous cellular component, have the same role in other organisms, including humans? What is the mechanism of its action? One can think of many others. However, the number of questions that now come to mind is a proof that the study by Gray et al. truly changes the way we think of protein quality control.

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