Elucidating the activation mechanism for GBP1 oligomerization – a key player in innate immunity against microbial pathogens

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The dynamin-related human guanylate-binding protein 1 (GBP1) mediates host defense against microbial pathogens. Upon GTP binding and hydrolysis, auto-inhibited GBP1 monomers dimerize and assemble into soluble and membrane-bound oligomers, which are crucial for innate immune responses. How higher-order GBP1 oligomers are built from dimers and how assembly is coordinated with nucleotide-dependent conformational changes has remained elusive. Here, we use cryo-electron microscopy and a detailed biochemical analysis to elucidate the activation mechanism of GBP1 leading to oligomerization and encapsulation of bacterial pathogens. We present cryo-electron microscopy-based structural data of the soluble and membrane-bound GBP1 oligomers demonstrating that GBP1 assembles in an outstretched dimeric conformation. By combining new and published structural insights with biochemical, mechanistic, and pathogen-based data, our study provides the molecular basis for understanding GBP-mediated antimicrobial functions. We identify a surface-exposed helix in the large GTPase domain, which contributes to the oligomerization interface, and probe its nucleotide- and dimerization-dependent movements facilitating the formation of an antimicrobial protein coat on a Gram-negative bacterial pathogen. Our results reveal a sophisticated activation mechanism for GBP1 in which nucleotide-dependent structural changes coordinate dimerization, oligomerization, and membrane binding to allow encapsulation of pathogens with an antimicrobial protein coat. In this way, our structure-function study deepens our understanding of the underlying molecular coupling of the GTPase cycle and oligomerization within the GBP protein family which is crucial for its antimicrobial functions.