Molecular Dynamics Investigations of Actin Mutations and their Role in Disease

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In Short

- ACTB and ACTG1 encode the cytoskeletal isoforms of actin
- Cytoskeletal actin participates in essential processes requiring the generation of intracellular chemomechanical force and translocation of cargo
- Cytoskeletal actin dynamics and function functions are finely regulated involving over one hundred interaction partners
- Mutations in ACTB and ACTG1 cause syndromic autosomal-dominant disorders
- Molecular Dynamics simulations are used to scan the conformational space of mutant actin with the aim to reveal underlying disease mechanisms

Actin is one of the most abundant proteins in eukaryotic cells. Over a hundred interaction partners of actin are known to date that regulate its dynamics and functions, including the interaction with other actin molecules in the formation of filaments. Due to its ability to polymerize and form various higher order structures, ranging from single filaments, to highly organized bundles and networks, it performs a large variety of functions. Actin supports cellular processes including endocytosis, intracellular transport, cytokinesis, migration and the definition of cell shape. The structure of actin plays a crucial role in these interactions [1], figure 1. Consequently, it is not surprising that even small structural changes induced by missense mutations can perturb these interactions and act as disease triggers. A multitude of diseases caused by point mutations in the six human actin isoforms has been reported [2]. Mutations in the two cytoplasmic genes, ACTB and ACTG1, show strong diversity in terms of resulting disease phenotypes (for examples see figure 1) [2–5]. Pathological conditions are frequently linked to changes in filament nucleation, elongation or turnover that are caused by structural changes affecting actinâactin or actinâactin binding protein interactions, nucleotide binding or ATP hydrolysis. Certain effects are the result of specific mutations that lead to a particular disease phenotype. In some cases, the location of the affected amino acids suggests a common disease mechanism. The molecular basis of a shared molecular disease mechanism is not so obvious when different mutations cause the same effect e.g. do not allow for correct folding, completely disrupt an interaction, or change the stability of the protein [5,6].

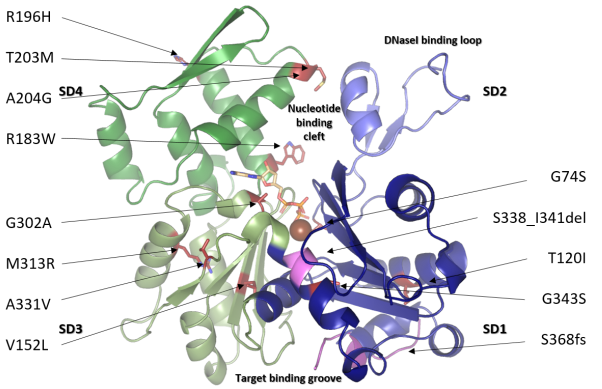

***Figure 1:** Structure of human cytoplasmic actin (PDB-ID: 2btf). Selected mutations causing actinopathies are depicted: point mutations in red, the helical turn of the deletion mutant S338_I341del in pink and the Alphafold predicted structural difference of the S368fs mutant purple.*

Several of the actinopathy-causing mutations in the two human cytoplasmic actin isoforms have been studied extensively in vitro and partially in vivo [2]. Our approach is based on combining experimental results obtained from the biochemical and biophysical characterization of mutant ACTB and ACTG1 proteins with long-time MD-simulations for the elucidation of parameters that describe the conformational behavior of actin monomers with respect to protein-stability and actin-interactions. Such a detailed analysis will help us elucidate the extent to which mutations that bring about similar functional consequences are related to the observed disease phenotypes. Moreover, this approach will allow us to make predictions on the impact of mutations for which patient-derived cells from biopsies are currently not available.

WWW

https://www.mhh.de/bpc

More Information

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Project Partners

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Funding

European Joint Programme on Rare Diseases funded research project: ejprd19-033_project