P-1.39

Integrative Characterisation of Ex Vivo Pathological Samples in the Study of a Disease-associated Protein Aggregation Pathway

James Irving [1], Sarah Lowen [1], Ibrahim Aldobiyan [1], Sarah Vickers [1], Christopher Waudby [1], John Christodoulou [1], Konstantinos Thalassinos [1], David Lomas [1]

[1] University College London, London, United Kingdom

We have characterised the disease-associated aggregation pathway of α1-antitrypsin, a member of the serpin family of protease inhibitors, that is expressed at high levels by hepatocytes and abundant in the plasma where it protects tissue from damage by neutrophil elastase. In the presence of certain mutations, α1-antitrypsin accumulates in the liver as dense intracellular deposits; these are the consequence of a non-amyloid ordered aggregation that yields unbranched protein polymers, that are both extremely stable and functionally inactive.

Using orthogonal structural and biophysical techniques applied to protein extracted from human-derived samples, we have defined molecular details of the serpin polymerisation pathway. Our data support a mechanism whereby α1-antitrypsin progresses through distinct states as it transitions from a mildly-perturbed monomeric intermediate to a hyperstable polymeric form whose subunits have undergone an intra and intermolecular reconfiguration. This has allowed us to draw conclusions regarding transient species on the pathway and the likely mechanism by which the barrier to conformational change is circumvented. The commonalities between mechanistic function and pathological malfunction reveal a molecule that is poised between these opposing outcomes.