Serpin polymerisation: neuroserpin and alpha-1 antitrypsin related diseases

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The superfamily of the serin protease inhibitors (serpins) includes an ample group of proteins characterised by a high degree of homology and a unique mechanism of inhibition, where the serin protease is attracted by a target site in the serpin’s reactive centre loop. Upon cleavage, the protease remains covalently linked to the serpin, which undergoes a strong conformational transition where the reactive centre loop inserts into the main beta sheet of the serpin. This releases energy that is used to destroy the conformation of the active site of the protease, which is irreversibly inhibited. This mechanism requires a high flexibility from the serpins, which are very sensitive to point mutations that increase their natural instability, leading to misfolding and polymerisation. Polymers of secretory serpins remain stack in the endoplasmic reticulum (ER) of the cell of synthesis, causing ER stress and eventually cell death. This is the molecular basis for several human diseases known collectively as the serpinopathies, which are characterised by the presence of inclusion bodies made of polymers and a double disease phenotype: problems caused by the lack of active serpin in the place of action (loss of function), and problems caused by the accumulation of polymers in the place of synthesis (toxic gain of function). Two serpinopathies are better known, alpha-1 antitrypsin deficiency and the dementia FENIB (familial encephalopathy with neuroserpin inclusion bodies). The second one is due to point mutations in neuroserpin, which is mainly expressed by neurons. Our work has demonstrated that four of the mutations that cause FENIB lead to neuroserpin polymerisation and retention in the ER (figure), in a degree that correlates directly with the severity of the disease caused by each mutation, and that these polymers are toxic *per se* in a Drosophila model of FENIB.

