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Molecular basis of systemic amyloidosis caused by β2-microglobulin

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Dialysis related amyloidosis (DRA) is a severe complication in patients who have undergone haemodialysis for more than ten years. The deposition of amyloid fibrils in the osteo-tendineous system causes the onset of the disease. Full-length β_2m and its truncated fragment lacking in the first 6 residues (ΔN6β_2m) are the main protein constituents of this type of fibrils. Although the most important risk factor for DRA is the increase in the blood levels of β2-m over a long period, the molecular mechanism is not yet well known. Our studies have pointed out that three components: collagen, glycosaminoglycans (in particular heparin) and the truncated form ΔN6β_2m, represent a key factor for the amyloid conversion of β_2m (1,2). Our recent data envisage a model of "nucleation dependent" fibrillogenesis near the collagen surface where soluble β_2-m oligomers represent the species that most avidly bind the collagen surface and are capable of speeding up the kinetics of fibrillogenesis.
Combining dynamic light scattering with atomic force microscopy we can now monitor the formation of pre-fibrillar oligomers under established conditions. We will be able to investigate the overall conformation of the aggregate alongside the type of all the intermolecular interactions involved. For this purpose chemical cross linkers must be used to stabilise the oligomers. We have discovered that some cross linkers can stabilize oligomers and fibrils without altering their structural and functional properties (3). This approach will be used to elucidate structure and function of isolated and homogeneous oligomeric species. Furthermore, our preliminary results, obtained in collaboration with the group of Prof. Stefani at the University of Florence, show that oligomerized β2-m is cytotoxic towards a neuroblastoma cell line at β2-m concentrations that can be easily reached in the plasma of haemodialysed patients.

References

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