Which is the most toxic species in the aggregation pathway of transthyretin?

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Wild type transthyretin (TTR) has been involved in senile systemic amyloidosis (SSA) while more than 100 variants have been associated with familial amyloidotic polyneuropathy (FAP). There is a debate in the literature concerning the identification of the toxic species present in the pathway to fibril formation (native → protofibril → fibril). In the current study, we are investigating the cytotoxicity of the different aggregates of the wild-type TTR, and its variants using neuroblastoma cells. Aggregates are being produced either by acidification or after a cycle of compression-decompression. The MTT assay shows that after centrifugation the supernatant of the samples were more toxic than the pellet to these cells. These results suggest that the smaller aggregates present in the supernatant would be responsible for the dysfunction observed in the patients with FAP and SSA. Interestingly, aggregates present in the supernatant of the aggressive variant L55P showed to be the most cytotoxic, even at neutral pH. The species present in the pellet has a strong capacity to bind Congo Red, an amyloid marker, in contrast with the supernatant, confirming the absence of mature amyloid fibrils in the supernatant of these solutions. Now we are characterizing the morphology and the size of these toxic species by size exclusion chromatography and AFM.

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