

Commentary

Research Highlights

Green Tea Catechin Antagonizes Amyloid-Related Toxicity

Bieschke, J.; Russ, J.; Friedrich, R.P.; Ehrnhoefer, D.E.; Wobst, H.; Neugebauer, K.; Wanker, E.E. EGCG remodels mature alpha-synuclein and amyloid-beta fibrils and reduces cellular toxicity. *Proc. Natl. Acad. Sci. USA*, **2010**, *107*, 7710-7715.

Age-related neurodegenerative diseases represent a growing socio-economic burden to developed societies due to an increased life-expectancy and the lack of effective treatments. The pathological hallmarks of the majority of these diseases, including Alzheimer's (AD) and Parkinson's disease (PD), are proteinaceous inclusions and the progressive loss of neurons. These inclusions are characterised by β -sheet-rich fibrillar aggregates commonly termed amyloids that accumulate in the extracellular milieu or intracellular compartments of affected neurons. Protein aggregates are commonly derived from misfolded proteins that are prone to amyloidogenesis due to structural modifications, such as mutant forms of α -synuclein (in PD) or aberrantly cleaved forms of amyloid precursor protein (A β in AD). Amyloidogenesis occurs when the normally reversible balance between monomers and oligomers destabilises towards the predominant formation of oligomers, which subsequently undergo a conformational conversion into amyloid fibrils. Although still debated, the prevalent hypothesis is that amyloid fibrils represent a cellular protection mechanism, whereas soluble intermediate oligomeric and pre-fibrillar protein species are the major cause of cellular toxicity. However, the precise mechanism(s) leading to cell death are not understood. Despite this, there is an urgent need for new therapeutic strategies aimed at slowing or halting the progression of neurodegenerative diseases.

A significant contribution in this direction has been the discovery that catechins derived from green tea are potent inhibitors of protein fibrillarization. Namely, epi-gallocatechin-3-gallate (EGCG) has been shown to antagonise both the formation of aggregates and the cellular toxicity of several aggregation-prone proteins including α -synuclein and A β . These studies already showed that EGCG can prevent amyloidogenesis, at least in cell-based model systems. The potential clinical application of such a drug could be to halt, or at least slow disease progression. However, because the majority of proteinopathies are sporadic, they are usually diagnosed once clinical symptoms have become apparent due to the loss of large populations of nerve cells. The evident question then arises whether EGCG might also be effective in disassembling toxic aggregation intermediates. To address this question, Erich Wanker and colleagues used *in vitro* aggregation assays and cell-based models of disease to demonstrate that *EGCG remodels mature α -synuclein and A β fibrils and reduces cellular toxicity*. Following on their previous work on EGCG, Bieschke *et al.* now show that EGCG affects the ordered fibrillar structure of α -synuclein and A β aggregates, leading to amyloid remodelling. They show that EGCG binding to aggregates precedes, and is necessary and sufficient for structural change. Most importantly, this study provides evidence that EGCG treatment remodels toxic β -sheet-rich amyloid protofibrils into smaller amorphous protein aggregates, thereby reducing cellular toxicity. The authors then tested several other EGCG-related polyphenols and found that the gallate moiety present in a variety of green tea catechins harbours the critical structural module required for efficient amyloid conversion from toxic proto-fibrils into amorphous, benign protein aggregates.

The work by Bieschke *et al.* increases our understanding of the causes underlying amyloid-driven neurodegeneration, and demonstrates a potential therapeutic benefit of gallate in neurodegenerative diseases characterised by the formation of amyloid lesions. The fact that gallate can change the properties of amyloids from being neurotoxic to benign should make it a vital tool that allows further dissection of the structural and molecular basis of amyloid toxicity. In addition, this report represents a major step towards the identification of drugs with the potential to target proteinopathies. So far, the efficacy of EGCG has been shown *in vitro* and in cell-based model systems, but also in fly models of Huntington disease. The next step, of course, will be to show whether this holds true also for mammalian *in vivo* models, with the ultimate goal (and hope) that EGCG will be successful in clinical trials.

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