Design and synthesis of transglutaminase inhibitors as potential therapeutic agents for neurodegenerative disease

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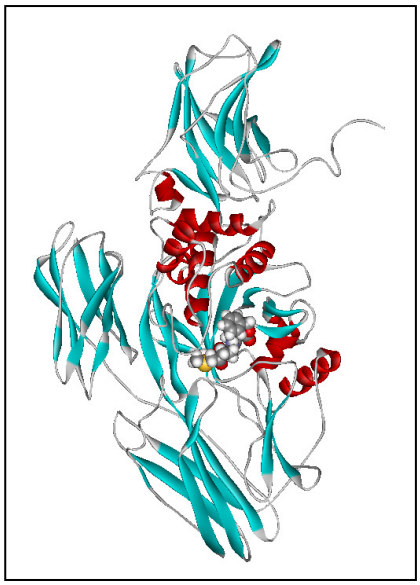
The design and synthesis of selective transglutaminase inhibitors capable of crossing the blood-brain barrier will be undertaken with a view to developing novel drug treatments for age-related neurodegenerative disease. This project will comprise synthetic chemistry predominantly but will also include molecular modelling and some basic enzyme assays.

Background



Transglutaminases (TGases) catalyse the calcium-dependent crosslinking between proteins through formation of a peptidase-stable isopeptide linkage between glutamine and lysine residues on separate protein molecules. [1, 2] This is the heart of a generic biological tissue stabilization process. Blood clot stabilization and wound healing,[3] for example, are facilitated by this process. There are occasions, however, when it would be beneficial to block this otherwise natural process example include fibrosis and scarring, thrombosis and neurodegenerative diseases such as Alzheimer's and Huntington's.[4, 5] Protein aggregates in affected brain regions are histopathological hallmarks of many neurodegenerative diseases. It is thought that transglutaminase (TGase) activity might contribute to the formation of protein aggregates in Alzheimer's disease (AD) brain. Tau protein has been shown to be an excellent substrate of TGases and cross-links have been found in the neurofibrillary tangles and paired helical filaments of AD brains. In addition, there is evidence that TGases contribute to the formation of proteinaceous deposits in Parkinson's disease (PD) and in Huntington's disease (HD). The development of selective TGase inhibitors capable of crossing the blood-brain barrier may lead to diagnostic and therapeutic tools for these neurodegenerative diseases.

Plan of Work

As a starting point we have several potent TGase inhibitors that are specific for TG2 over FXIIIa together with computer models of the same enzymes.[6] Molecular modelling will be used to design selective lipophilic analogues of the current TG2 lead inhibitors and these will be prepared by the student. The compounds will be screened against a panel of TGases and cell toxicity studies undertaken on human neuroblastoma cells. Enzyme inhibition results will feed into the design of further compounds for further rounds of synthesis and screening.

References

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