Understanding how the Alzheimer's Amyloid Presursor Protein binds Copper Ions

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Alzheimer's disease is a debilitating neurodegenerative disorder. Soluble oligomers of Aβ peptides are neurotoxic and thought to trigger the development of the disease. The interaction between copper (Cu) ions and the transmembrane amyloid precursor protein (APP) in the brain may play a key role in modulating the pathogenesis. The binding of extracellular Cu^{2+} to APP in vitro lowers the processing of APP into Aβ When Cu^{2+} is supplemented in their diet, transgenic mice over-producing Aβ had improved survival and decreased soluble Aβ level. However, the administration of significant amounts of Cu^{2+} in humans is likely to cause toxic side-effects. Structural studies of Cu^{2+} binding to APP will therefore aid development of suitable Cu^{2+} mimetics for use in treating the disease.

The APP interacts with and reduces Cu^{2+} ions through the extra-cellular copper binding domain (CuBD). The crystal structure of CuBD in metal-free (apo) form is determined to 0.85 Å resolution using X-ray diffraction data at a synchrotron. The structure of CuBD bound with Cu^{2+} was obtained from apo crystals soaked in a solution containing $CuCl_2$, and a pursuant reduction step generated the Cu^{+}-bound structure. In both cases, the Cu ion is coordinated to His147, His151, Tyr168 and a water molecule, in a distorted square planar geometry. As the water ligand might represent an amino acid ligand from another APP domain or between APP molecules, X-ray absorp-tion spectroscopy of Cu binding in solution is being pursued while longer APP constructs covering the CuBD are studied and crystallised.

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