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# MOLECULAR AND CELLULAR PATHOLOGY OF NEURODEGENERATIVE DISEASE

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Alzheimer's, Parkinson's and Motor neurone diseases are all the consequences of selective neuronal death. The corresponding vulnerable neurones in these diseases all exhibit characteristic cytopathologies which have certain common features.

The principal neuronal inclusion of Alzheimer's disease is the neurofibrillary tangle. Ultrastructurally, tangles are seen to be aggregates of paired helical filaments (PHF). Immunochemical and protein chemical studies have demonstrated that PHF are derived from several cytoplasmic proteins: the microtubule-associated proteins, $\tau$ and MAP 2, neurofilaments, and ubiquitin. There is also circumstantial evidence that $\tau$ and neurofilaments are abnormally phosphorylated.

In the case of Parkinson's disease, Lewy bodies are also apparently formed from cytoskeletal proteins. Neurofilaments but not $\tau$ nor MAP 2 have consistently been found to be present in Lewy bodies and these Lewy body-associated neurofilaments may too be abnormally phosphorylated. Ubiquitin is also present in the Lewy body.

Motor neurone disease has recently been found to exhibit unusual inclusion bodies in the spinal cord anterior horn cells that so far have only been labelled by ubiquitin antibodies. It remains to be seen if these inclusion bodies are also cytoskeletal in origin. However, these ubiquitin inclusion bodies do appear to be an excellent diagnostic marker of motor neurone disease.

In addition to the neurofibrillary tangles in Alzheimer's disease, senile plaques are a major histopathological hallmark of the disease. Senile plaques consist of an extracellular core which is partly inorganic in character, being aluminosilicate, and partly proteinaceous. The protein component is the A 4 or $\beta$-amyloid protein which is a polypeptide of 42 amino acids and molecular weight of 4200. This protein is derived from a larger precursor of around 700 amino acids which seems to be a membrane protein. The mechanism by which A 4 amyloid protein is produced from the precursor has still to be elucidated.

There are several types of senile plaque morphologies and it is usually assumed that they represent different stages in development. A recently described senile plaque, termed plaque A, appears to be a region of altered neuropil texture with a central cell, probably a microglial cell. This suggests that plaques A may be caused by the abnormal behaviour of microglia.

Staining of senile plaques with antibodies has begun to reveal something of the biochemical processes that accompany plaque development. Senile plaques with an extracellular core are labelled in the core by antibodies to the A4 protein and antibodies to the heparan sulphate proteoglycan core protein; antibodies to $\alpha_1$-antichymotrypsin label plaques in the periphery. Antibodies to A4 after treatment of sections with formic acid have been found to label many "diffuse plaques" that have not previously been detected. Plaques A are also labelled by anti-A4, antiheparan sulphate proteoglycan core protein and antibodies to $\alpha_1$-antichymotrypsin; plaques A and diffuse plaques may be identical or be similar since they do not contain large deposits of amyloid nor dystrophic neurites. These plaques may represent the earliest stage of plaque development in which the extracellular matrix of the neuropil is one of the first structures to become abnormal, however, whether all such plaques go on to develop into classical neuritic plaques is not clear.