Biol212 Biochemistry of Disease

Neurological Disorders: Alzheimer's disease
Alzheimer's disease

- Alzheimer's disease (AD) accounts for 50-70% of late-onset (after age 65) cases of dementia.
- Progressive decline in cognitive function that eventually leaves patients bedridden.
- Major risk factor is increasing age.
- Two neuropathological lesions - senile plaques and neurofibrillary tangles, provide a definitive diagnosis of AD after a patient's death.
Brain scans done with Positron Emission Tomography (PET) show how Alzheimer’s affects brain activity. The left image shows a normal brain, while the right is from a person with Alzheimer’s. The blue and black areas in the right image indicate reduced brain activity resulting from the disease.

*Images courtesy of Alzheimer’s Disease Education and Referral Center, National Institute on Aging*
Senile plaques

Senile plaques consist of aggregates of \textit{amyloid }\textit{\( \beta \)-peptides} (A\( \beta \)). These peptides are proteolytically cleaved from the amyloid precursor protein (APP) by two proteases, \( \beta \)-secretase and \( \gamma \)-secretase.
Intraneuronal tangles

- Intraneuronal tangles consist primarily of aggregates of hyperphosphorylated tau protein.

- Other tau post-translational modifications include ubiquitination and glycosylation.

- Mutations in tau have been identified in other neurological diseases, where they cause dementia and tangles without plaques.

(left) A neuron in AD brain tissue containing a neurofibrillary tangle (*).
(right) An enlarged view of a portion of the tangle area (*)(sections immunogold-labelled for tau protein).
**Amyloid β-peptides**

- The two major isoforms of Aβ are Aβ$_{40}$ and Aβ$_{42}$, which have identical N-termini, but Aβ$_{42}$ is two residues longer.
- Aβ$_{42}$ is relatively insoluble and forms the major component of senile plaques.
- All known genetic factors predisposing to AD are related to the amyloid phenotype.
- Point mutations have been identified in three different genes which cause AD.


- **APP** - All disease-causing mutations map within or near the region encoding Aβ. In each case the mutation enhances production of Aβ42.

- **Presenilins** - Mutations in presenilin 1 (PSEN1) and presenilin 2 (PSEN2) also cause early-onset familial AD. The presenilins are transmembrane proteins that control the proteolytic processing of a number of integral membrane proteins, including APLP-1 a homologue of APP. In some way, the AD-linked mutant presenilin proteins also affect APP processing and increase Aβ42 production.

- **Apolipoprotein E4** - A major risk factor for late-onset AD is the occurrence of the apolipoprotein E*4 (APOE*4) isoform. The enzyme may show differential binding to Aβ and subsequent enhancement of aggregation.
Amyloid-cascade hypothesis

- In early-onset AD, overproduction of Aβ$_{42}$ directly triggers the pathogenic cascade.
- In sporadic cases, Aβ$_{42}$ produced in excessive quantities, cleared too slowly, or in contact with aggregation factors forms aggregates.
- This leads to the formation of senile plaques and initiates immunological and neurotoxicological cascades resulting in the pathological and clinical manifestations of AD.
(1) Overproduction, decreased clearance or enhanced aggregation of Aβ42

(2) Deposition of aggregated Aβ42 as diffuse plaques

(3) Aggregation of Aβ40 onto diffuse Aβ42 plaques

(4) Inflammatory response: microglial activation and cytokine release, astrocytosis and acute-phase protein release

(5) Progressive neuritic injury within amyloid plaques, disruption of neuronal metabolic homeostasis, oxidative injury

(6) Altered kinase/phosphatase activities, tau hyperphosphorylation and tangle formation

(7) Widespread neuronal dysfunction and death in hippocampus and cortex with progressive neurotransmitter deficits

(8) Dementia
The secretases

- Blocking the proteolytic machinery that generates Aβ$_{42}$ is an attractive therapeutic option.

- On its way to the cell surface, two different proteases α- and β-secretase can cleave at different positions in APP leading to the release of the large soluble N-terminal fragments α-APPs and β-APPs, respectively.

- Cleavage by α-secretase occurs within the region containing Aβ and, thus, precludes formation of Aβ$_{42}$.

- In contrast, β-secretase action generates the free N-terminus of Aβ and is therefore considered to be the first critical step in amyloid formation.

- The membrane-bound C-terminal cleavage products (C99 and C83) produced by α- or β-secretase can be further acted upon by γ-secretase.

- This leads to the release and secretion of Aβ from C99 and p3, a shortened, non-pathogenic peptide from C83.

- The majority of γ-secretase action occurs at either residue 40 or 42 leading to the formation of Aβ$_{40}$ and Aβ$_{42}$ from C99, and p3$_{40}$ and p3$_{42}$ from C83.
APP

\[ \alpha \text{-APPs} \rightarrow C83 \rightarrow \gamma \text{-secretase} \rightarrow p3 \]

\[ \beta \text{-APPs} \rightarrow C99 \rightarrow \gamma \text{-secretase} \rightarrow A\beta \]
A novel transmembrane protein termed β-site APP cleaving enzyme (BACE) with the properties of β-secretase has been identified.

*PSEN1*-knockout mice have an 80% reduction in γ-secretase activity i.e. presenilin 1 is involved in cleavage by γ-secretase - it may itself be γ-secretase or it may be an essential part of the macromolecular complex, which catalyses γ-secretase activity.

Should be possible to generate secretase-specific protease inhibitors that penetrate the blood-brain barrier.

Use could be extended to include prevention of the disease in carriers of risk factors or even the general population above a certain age.
Ginkgo biloba is a plant extract reported to have benefits in the treatment of Alzheimer's disease - it may prevent oxidative damage caused by amyloid β-peptides.
Amyloidosis is a group of protein misfolding diseases in which protein aggregates (amyloid deposits) accumulate.

Summary of protein folding diseases and the related proteins and peptides in humans.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Associated proteins</th>
<th>Affected tissues</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amyloidosis—systemic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary systemic amyloidosis</td>
<td>Ig light chain</td>
<td>Most tissues</td>
<td>52</td>
</tr>
<tr>
<td>Ig heavy-chain-associated amyloidosis</td>
<td>Ig heavy chain</td>
<td>Most tissues</td>
<td>99</td>
</tr>
<tr>
<td>Secondary (reactive) systemic amyloidosis</td>
<td>SAA</td>
<td>Most tissues</td>
<td>100</td>
</tr>
<tr>
<td>Senile systemic amyloidosis</td>
<td>Transferrin</td>
<td>Microvasculature</td>
<td>11</td>
</tr>
<tr>
<td>Hemodialysis-related amyloidosis</td>
<td>ß2-Microglobulin</td>
<td>Osteoarticular tissues</td>
<td>101</td>
</tr>
<tr>
<td>Hereditary systemic ApoAI amyloidosis</td>
<td>ApoAI</td>
<td>Liver, kidney, heart</td>
<td>102, 103</td>
</tr>
<tr>
<td>Hereditary systemic ApoA II amyloidosis</td>
<td>ApoA II</td>
<td>Kidney, heart</td>
<td>103, 104</td>
</tr>
<tr>
<td>Finnish hereditary amyloidosis</td>
<td>Gelatin</td>
<td>Most tissues</td>
<td>105</td>
</tr>
<tr>
<td>Hereditary lysozyme amyloidosis</td>
<td>Lysozyme</td>
<td>Kidney, liver</td>
<td>106</td>
</tr>
<tr>
<td>Hereditary cystatin C amyloid angiopathy</td>
<td>Cystatin C</td>
<td>Most tissues</td>
<td>107</td>
</tr>
<tr>
<td><strong>Amyloidosis—localized</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection-localized amyloidosis</td>
<td>Insulin</td>
<td>Skin, muscles</td>
<td>108</td>
</tr>
<tr>
<td>Hereditary renal amyloidosis</td>
<td>Fibrinogen</td>
<td>Kidney</td>
<td>109</td>
</tr>
<tr>
<td>Senile renal vessel amyloid</td>
<td>Lactoferrin, semenogelin</td>
<td>Seminal vessels</td>
<td>110, 111</td>
</tr>
<tr>
<td>Familial subepithelial corneal amyloidosis</td>
<td>Lactoferrin</td>
<td>Cornea</td>
<td>112</td>
</tr>
<tr>
<td>Cataract</td>
<td>Crystalin</td>
<td>Eye</td>
<td>113</td>
</tr>
<tr>
<td>Medullary thyroid carcinoma</td>
<td>Calcitonin</td>
<td>Thyroid tissues</td>
<td>114</td>
</tr>
<tr>
<td><strong>Neurodegenerative diseases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>Amyloid-ß, tau</td>
<td>Brain</td>
<td>115, 116</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>α-Synuclein</td>
<td>Brain</td>
<td>117</td>
</tr>
<tr>
<td>Lewy-body dementia</td>
<td>α-Synuclein</td>
<td>Brain</td>
<td>118</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>Huntington</td>
<td>Brain</td>
<td>119</td>
</tr>
<tr>
<td>Spongiform encephalopathies</td>
<td>Prion</td>
<td>Brain, peripheral nervous system</td>
<td>120, 121</td>
</tr>
<tr>
<td>Hereditary cerebral hemorrhage with amyloidosis</td>
<td>Cystatin C</td>
<td>Cerebral vasculature</td>
<td>122, 123</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>Superoxide dismutase 1</td>
<td>Brain</td>
<td>124</td>
</tr>
<tr>
<td>Familial British dementia</td>
<td>Abri</td>
<td>Brain</td>
<td>125</td>
</tr>
<tr>
<td>Familial Danish dementia</td>
<td>ADα, amyloid-ß</td>
<td>Brain</td>
<td>126</td>
</tr>
<tr>
<td>Familial amyloidotic polyneuropathy</td>
<td>Transferrin</td>
<td>Peripheral nervous system</td>
<td>127</td>
</tr>
<tr>
<td>Frontotemporal dementias</td>
<td>Tau</td>
<td>Brain</td>
<td>128</td>
</tr>
<tr>
<td><strong>Other diseases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes melitus</td>
<td>IAPP, amylin</td>
<td>Pancreas (islet)</td>
<td>129</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>Modified LDL</td>
<td>Arteries</td>
<td>130</td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td>Hemoglobin</td>
<td>Erythrocytes</td>
<td>131, 132</td>
</tr>
</tbody>
</table>
Parkinson’s Disease

- Parkinson's disease (PD), like AD, is a common neurodegradative disease that leads to movement disorder, resting tremor and rigidity.
- Like AD, protein deposits are seen in selected neuronal populations.
- Specifically, PD is associated with fibrillar cytoplasmic inclusions in dopaminergic neurons of the substantia nigra.
- These inclusions are known as **Lewy bodies** and mainly contain ubiquitin and **a-synuclein**.
- Familial PD has been linked to mutations in the gene encoding a-synuclein (both ala30pro and ala30thr mutations lead to enhanced protein aggregation); however, the cause of the more commonly encountered sporadic disease remains unknown.
Huntington's Disease

Huntington’s disease (HD) is a progressive neurodegenerative disorder with autosomal dominant inheritance.

It is characterised by selective neuronal cell death, primarily in the cerebral cortex and striatum, which leads to psychiatric symptoms, motor impairment and dementia.

HD is caused by the presence of elongated polyglutamine (polyQ) sequences in a protein huntingtin.

The formation of insoluble polyQ-containing protein aggregates (also containing ubiquitin) in neuronal inclusions has been detected in post-mortem brains of patients.
HD, PD, AD and prion diseases are all based upon an aggregation-based pathological mechanism.

The first step in the process is a conformational change in a disease protein leading to β-sheet formation.

This process may be facilitated by a mutation, but other events such as proteolytic cleavage or binding of chaperones might also contribute to the destabilization of the disease protein.

Once a structure rich in β-sheets has formed, protein aggregates are formed that are protease-resistant and toxic for neuronal cells.

The pathogenesis of these diseases may be linked to the recruitment of various proteins (e.g. transcription factors) into insoluble aggregates of the respective disease protein.
Mutations

- Chaperones
- Proteolytic cleavage
- Interacting proteins

Native conformation

β-Sheet structure

Fibrillar aggregates

- Recruitment of transcription factors, chaperones and/or caspases into insoluble aggregates
- Membrane damage; Generation of free radicals
- Resistance to proteolysis; Inhibition of the ubiquitin/proteasome pathway

Altered signal transduction

Apoptosis?

Cell death?

Intracellular inclusions

Molecular Medicine Today
Alzheimer's disease (AD) is characterised by two neuropathological lesions - *senile plaques* and *neurofibrillary tangles*.

Senile plaques consist of aggregates of proteasae-resistant *amyloid β-peptides* and tangles consist primarily of aggregates of *hyperphosphorylated tau* protein.

All known genetic factors predisposing to AD are related to the amyloid phenotype.

Blocking the proteolytic machinery that generates Aβ is an attractive therapeutic option. It should be possible to synthesize secretase-specific protease inhibitors that penetrate the blood-brain barrier.

Parkinson's disease, like AD, is a common neurodegradative characterised by neuronal inclusions known as *Lewy bodies* that contain ubiquitin and α-synuclein.

Huntington's disease is caused by the formation of insoluble polyQ-containing protein aggregates (also containing ubiquitin) in neuronal inclusions.