ALZHEIMERS

• A disease of aberrant cleavage of a protein during proteolytic processing
• Leading to misfolding
• Leading to aberrant aggregation.
Cleavage of APP by secretases:
Schematic of plaque formation between nerve cells
The Tau, beta amyloid....mitochondrial connection.
DISEASES OF ER STRESS
Amino acids
Glucose deprivation

Perk
Hormone signals

GCN2

heme

HRI

Virus defence

PKR

eIF2alpha

Pi
CYSTIC FIBROSIS: MUTATION OF THE CHLORIDE CHANNEL.
STRUCTURE OF CFTR
THERE ARE OVER 100 DIFFERENT MUTATIONS OF CFTR (95% OF PATIENTS HAVE THE SAME ONE)

- **Five functional classes of CF mutations have been described**
  - **Class 1 mutations**
    - Defective protein production with premature termination of CFTR production. Class 1 mutations produce few or no functioning CFTR chloride channels.
  - **Class 2 mutations**
    - Defective trafficking of CFTR so that it does not reach the apical surface membrane where it can function.
Class 3 mutations
Defective regulation of CFTR even though it is able to reach the apical cell surface.

Class 4 mutations
CFTR reaches the apical surface but chloride transport through the channel is defective.

Class 5 mutations
Reduced production of functional CFTR. A small amount of functional CFTR may reach the surface.
The F508del CFTR mutation impairs CFTR processing in the endoplasmic reticulum (ER) by preventing the protein from folding properly. Misfolded F508del-CFTR is retained by the ER and degraded, reducing F508del-CFTR delivery to the cell surface.
• In addition, the small amount of F508del-CFTR that is delivered to the cell surface exhibits defective channel gating and increased turnover
Correction of the F508del-CFTR protein processing defect in vitro by the investigational drug VX-809

Fredrick Van Goora, Sabine Hadidaa, Peter D. J. Grootenhuisa, Bill Burtona, Jeffrey H. Stacka, Kimberly S. Straley, Caroline J. Deckera, Mark Millera, Jason McCartneya, Eric R. Olsonb, Jeffrey J. Winec, Ray A. Frizzellld, Melissa Ashlocke, and Paul A. Negulescua,1
Freidriechs ataxia

• Mitochondrial disease

Altered iron metabolism

Much increased oxidative stress and ROS production
FRATAxin
Fridreicht ataxia

\[(GAA)_{500}\]

FRATAxin

\textit{FRDA} exon 1 intron 1 exon 2

FRATAxin

\textit{FRDA}
• The genetic mutation (expansion of an intronic GAA triplet repeat in the FXN gene) leads to reduced expression of the mitochondrial protein frataxin. Over time this deficiency causes the nerve damage, as well as frequent fatigue due to effects on cellular metabolism.
FREIDRECHS ATAXIA.

Friedreich Ataxia: Molecular Mechanisms, Redox Considerations, and Therapeutic Opportunities
Renata Santos,1 Sophie Lefevre,1,2 Dominika Sliwa1, Alexandra Seguin,1 Jean-Michel Camadro,1 and Emmanuel Lesuisse1

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• Increasing Frataxin Gene Expression with Histone Deacetylase Inhibitors as a Therapeutic Approach for Friedreich's Ataxia

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• POLYGLUTAMATE REPEATS.

• From Huntingtons to Prion diseases.