Friedreich Ataxia Research and Prospects for Therapy

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Outline

• Friedreich Ataxia (FA)
• Frataxin
• Frataxin and Iron-Sulfur Cluster Synthesis
• FA Pathophysiology
• Emerging Treatments for FA
Friedreich Ataxia (FRDA)

- Autosomal recessive (~1:40,000)
- Progressive ataxia
- Hypertrophic cardiomyopathy (60%)
- Diabetes mellitus (30%)
- Muscle weakness, scoliosis
Friedreich Ataxia: Molecular Basis

Campuzano et al. 1996

FRDA

$\text{(GAA)}_{n>60}$ → Frataxin (210 aa) → Inhibition of mRNA synthesis → Frataxin depletion

- How is frataxin normally made?
- What does frataxin normally do?
- What happens when there is not enough frataxin?
- What can be done to ameliorate the disease?
Synthesis of Frataxin

1. **Nucleus**
   - mRNA
   - (GAA)n

2. **Cytoplasm**
   - Leader frataxin
   - Precursor

3. **Mitochondrion Matrix**
   - Protein Import
   - MPP
   - Processing

4. **Function**
   - Fe

5. frataxin
• What exactly is mitochondrial iron metabolism?

• And how does Frataxin relate to this process?
• DNA synthesis
• DNA repair
• Protein synthesis
• O₂ Transport
• Drug metabolism
• Oxidant defense
  ...

Mitochondrial Iron Metabolism

Fe-S

heme

Oxyphos

ATP

O₂⁻

H₂O₂

Fe²⁺

OH⁻
Biological Fe-S Clusters

<table>
<thead>
<tr>
<th>Structure</th>
<th>Oxidation state</th>
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<tbody>
<tr>
<td>[3Fe-4S]$^+$</td>
<td>[3Fe-4S]$^0$.</td>
</tr>
<tr>
<td>[4Fe-4S]$^{3+}$</td>
<td>[4Fe-4S]$^{2+}$.</td>
</tr>
<tr>
<td>[4Fe-4S]$^+$</td>
<td>[4Fe-4S]$^0$.</td>
</tr>
<tr>
<td>[8Fe-8S]$^{5+}$</td>
<td>[8Fe-8S]$^{4+}$.</td>
</tr>
<tr>
<td>[8Fe-7S]$^{3+}$</td>
<td>[8Fe-7S]$^{2+}$.</td>
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</tbody>
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John et al. *Annu Rev Biochem*
Fe-S Cluster Synthesis in Eukaryotes

Tracey A. Rouault & Wing Hang T
TRENDS in Genetics 2008
Fe-S Cluster-Containing Enzymes

Tracey A. Rouault & Wing Hang Tong

TRENDS in Genetics 2008
Frataxin promotes [2Fe-2S] Assembly on ISCU

\[
\text{ISCU} \quad + \quad \text{NFS1} \quad + \quad \text{L-Cys} \quad + \quad \text{ISD11} \quad + \quad \text{Human Frataxin} \quad + \quad \text{Iron}
\]
1. Frataxin (FXN) Deficiency

2. ↓ Mitochondrial Fe-S Enzymes

3. ↑ Free Cys, ↑ Fe$^{3+}$, ↑ Fe$^{2+}$, ↑ OH•, Cystine → H$_2$O$_2$

4. mtDNA Instability

5. ↓ ATP

6. ↓ Cellular Fe-S Enzymes

7. Nuclear Genome Instability
• Frataxin deficiency causes progressive accumulation of cellular damage.

• How can we stop this?
Therapeutic Targets in FA

Fe-S

Frataxin

HDACi (Pre-clinical)
EPO (Early clinical)
Protein replacement (Pre-clinical)

ROS

Fe

Idebenone (Phase III)
A0001 (Phase I)
Other antioxidants (Pre-clinical)

Deferiprone (Phase II)
Additional Iron Chelators (Pre-clinical)

Courtesy of R.
Other Approaches

- iPS Technology
- Gene Therapy
The promise of human induced pluripotent stem cells for research and therapy.

- Disease mechanisms
- Drug screenings
- Effects of new drugs
- Cell therapy

Nishikawa S, Goldstein RA, Nierras
Frataxin Deficiency

- DRG Neurons
- Cardiomyocytes
- Pancreas β Cells

FA iPS

Cell Death
No obvious negative effects

• Other Cells
Conclusions

FA results from low levels of the mitochondrial protein frataxin.

Frataxin plays an essential role in iron metabolism and in the protection from oxidative stress.

Emerging therapies target the negative effects of frataxin deficiency (e.g. ROS, toxic iron); they also target frataxin expression (e.g. HDAC inhibitors).

iPS technology for FA is also actively pursued in the research pipeline.